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Listeria monocytogenes meningitis in previously healthy adults

Christine J. Hearmon and Salil K. Ghosh

Department of Medicine and Infectious Diseases, General Hospital, Middlesbrough, Cleveland TS5 5AZ, UK.

Summary: A retrospective study of four sporadic cases of *Listeria monocytogenes* meningitis is reported. Contrary to the conventional epidemiology these patients were adults who were not immuno-compromised. Although all four cases produced positive cerebrospinal fluid cultures, in three, listeria was not microscopically identified. Protein and glucose contents of cerebrospinal fluids were variable and all samples showed lymphocytic pleocytosis. All four had neutrophil leucocytosis in peripheral blood.

The unwary may dismiss lymphocytic meningitis as being of 'viral' origin, thereby making an important diagnostic misjudgement of vital therapeutic importance.

Intravenous ampicillin is the drug of first choice for treatment of listeria meningitis; third generation cephalosporins are ineffective.

Introduction

Meningitis due to *Listeria monocytogenes* is infrequent, usually affecting the immuno-compromised, those at the extremes of life or the pregnant. The incidence of listeria infection is rising and increasingly more cases are occurring in the previously healthy population. There are no diagnostic stigmata and the initial examination of the cerebrospinal fluid may not be helpful. Thus, even if bacterial meningitis is suspected despite a lymphocytic cerebrospinal fluid, treatment with third generation cephalosporins (an increasingly prevalent therapeutic preference) may be started. This is, of course, inappropriate as *L. monocytogenes* is usually resistant.

Material and methods

The four cases reported here were obtained from the register of medical infectious diseases wards. The case notes were studied retrospectively with the permission of relevant consultants. Isolation reports of listeria between October 1978 and September 1987 by Middlesbrough Public Health Laboratory in 11 others were collected from the laboratory records. As clinical details of a number of these cases were unobtainable, it was decided to concentrate on the four cases of central nervous system (CNS) infection affecting previously healthy adults.

Correspondence: S.K. Ghosh, M.B.B.S., F.R.C.P. (Glas. & Edin.)
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Case reports

Case 1

A 57 year old man presented with a 4-day history of nausea, vomiting and frontal headache. He was pyrexial (38.5°) with photophobia and neck stiffness. Initially cerebrospinal fluid (CSF) examination revealed (Table I) lymphocytic pleocytosis, elevated protein, near normal glucose but was negative on microscopy and culture. Total leucocyte count in peripheral blood was 13.4×10^9/l with 86% neutrophils. An initial diagnosis of benign viral meningitis was made but the patient deteriorated becoming comatose. A second lumbar puncture revealed no organism by microscopy and a possible diagnosis of tuberculous meningitis was entertained until *L. monocytogenes* was grown on culture. Repeated blood cultures were sterile.

Intravenous penicillin was commenced but after a transient improvement the patient developed left hemiplegia, relapsed into deep coma and died despite sterile CSF culture one day before death. Request for post-mortem was refused.

Case 2

A 64 year old woman was admitted with a history of fever, photophobia, vomiting and confusion for 24 hours. She was pyrexial (38.5°C), jaundiced with a positive Kernig's sign, but doubtful neck stiffness. Leucocyte count in peripheral blood was 13.7×10^9/l with 98% neutrophils. Blood cultures were sterile.

CSF examination (Table I) revealed a lymphocytic pleocytosis with high protein and low glucose content. Microscopy of CSF was negative but *L. monocytogenes* was cultured. Liver function tests were grossly deranged suggesting hepato-cellular damage. Antibody tests against hepatoviruses were negative. Complete recovery followed intravenous ampicillin and gentamicin therapy.

Case 3

A 60 year old man presented with 48 hour history of severe headache, nausea, fever, rigor and increasing confusion. On admission he was pyrexial (39.5°C), dehydrated, photophobic and had definite neck stiffness. Total leucocyte count was 17.8×10^9/l with 89% neutrophils in peripheral blood. Blood culture produced no growth. CSF showed lymphocytic response, contained elevated protein and decreased glucose levels; microscopy revealed Gram-positive bacilli and *L. monocytogenes* was cultured (Table I).

Initial treatment with intravenous penicillin was changed to ampicillin and chloramphenicol because of poor response. He made a complete recovery.

Case 4

A 26 year old man presented with a one day history of headache, vomiting and fever. His temperature was 38°C and neck stiffness developed within a few hours of admission. Total leucocyte count in peripheral blood was 18.7×10^9/l with 91.9% neutrophils. *L. monocytogenes* was cultured from blood. CSF examination showed a lymphocytic pleocytosis, an elevated protein but normal glucose content; microscopy was negative and possibility of tuberculous meningitis was considered until *L. monocytogenes* was cultured from CSF 19 hours later. He was treated with intravenous ampicillin and chloramphenicol and made a complete recovery.

Discussion

Human listerial infection has been recognized since Henle's record in 1893 according to Lavetter and his colleagues.[1] Infections due to listeria are steadily increasing; laboratory reports in England and Wales rose from 39 in 1975 to 81 in 1984.[2] The Central Public Health Laboratory received 214 cultures in the year up to the end of November 1987, of which 130 cases (including 42 deaths) involved adults and juveniles (excluding pregnants).[3]

Ubiquitous listeria is widely distributed in nature and between 1%[4] and 5%[5] of the human population are faecal listeria excretors, rising to 29% in poultry workers.[6] Direct transmission from animals is well known to veterinary surgeons, abattoir workers and farmers. Vertical transmission from infected mother to fetus (transplacental, acquisition from vaginal canal or perineum) is common and circumstantial evidence of venereal transmission exists.[7] A hospital outbreak has been reported[8] which may have been due to cross-infection. However, listeriosis is probably most often a food borne illness.[9] Outbreaks of listeriosis (Canada 1981;[5] the USA, 1983[10] and 1985;[11] Switzer-

Table I CSF results in four reported cases of *Listeria monocytogenes* meningitis

Case	Appearance	WBC × 10^6/l	Lymphocytes % / Neutrophil %	Protein g/l (normal = up to 0.40)	Glucose mmol/l (normal = 2.2 to 4.4)	Microscopy	Culture result sensitive to
1a	Clear	130	60/40	0.7	3.3	No organism	No bacterial growth
1b	Clear	71	60/40	0.6	0.9	No organism	*L. monocytogenes* penicillin, gentamicin, cephradin, co-trimoxazole
2	Slightly turbid	270	90/10	6.92	1.0	No organism	*L. monocytogenes* ampicillin, gentamicin, chloramphenicol
3	Clear	710	50/50	1.14	1.1	Gram-positive bacilli	*L. monocytogenes* ampicillin, gentamicin, chloramphenicol
4	Clear	386	90/10	2.8	4.1	No organism	*L. monocytogenes* ampicillin, gentamicin chloramphenicol

land, 1987[12]) have been traced to contaminated coleslaw, milk, Mexican cheese and soft cheese (Vacherin Mont d'Or) respectively. A sporadic case of *L. monocytogenes* meningitis in England has been causally related to contaminated cheese.[13]

The rise in incidence of listeria infections probably follows the standard practice of food refrigeration for prolonged periods at 4°C. Primary isolation of listeria in clinical and environmental specimens is enhanced at this temperature[5,14] and may reach a high count in food above pH 5.5;[14,15] such food consumed uncooked or undercooked is an obvious source of infection. The source of infection in any of the sporadic cases reported here has not been specifically investigated because there was no appropriate geographic, occupational or contact history. No source of infection could be demonstrated in any of the 54 cases reported by Pollock *et al.*[16]

Like other facultative pathogens, listeria usually infects the very young, pregnant woman, the elderly and those with immuno-compromised state or chronic debilitating disease. Apart from CNS infections, other defined listerial illness includes miliary granulomatosis (granulomatosis infantisepticum), oculoglandular inflammation, 'typhoid listeriosis', endocarditis and cutaneous infection,[1] less frequent presentations are pneumonia, septicaemia, peritonitis, acute hepatitis and adult respiratory distress syndrome.[14] Our case 2 may have exhibited acute hepatic disease in addition to CNS involvement. Host resistance depends on cell-mediated immunity, particularly the macrophages and T cell function.[14]

Inapparent listeriosis is common in humans, especially in the female genital tract with partial immunity as a result; this may explain why the newborn is seriously affected by perinatal listeria infection but the mother escapes. On the other hand male genital contamination is rare, which may be responsible for the male preponderance[16] in meningitis due to listeria. Eighty-four percent are males in one report[1] and in our group three out of four with CNS involvement are males. Interestingly, listeria infection in acquired immune-deficiency syndrome is not unduly common.[14] Listeria infection in previously healthy adults (excluding pregnants) is comparatively rare; however, such cases have been reported,[13,17,18] mostly involving CNS.

L. monocytogenes is considered to be responsible for not more than 1% of bacterial meningitis cases in the United Kingdom.[19] The most frequent (60 to 80% of juveniles and adults[16]) human presentation of listeria infection has been due to the involvement of CNS which presents as meningitis in 90% of cases. Suppurative lesions of brain have been documented in the absence of meningitis.[16,17] Multiple small abscesses were found in some cases, most of whom were previously healthy; in contrast, less localized encephalitis and large cerebral abscesses were present only in the debilitated or the immunosuppressed. Case 1 presented here may have had a right cerebral lesion in the internal capsule area causing hemiplegia.

Confident diagnosis of CNS infection due to listeria is nearly impossible on clinical grounds as there are no pathognomonic stigmata to differentiate it from any other bacterial aetiology, particularly if the microbe is absent on CSF microscopy. Only one was microscopically positive out of five samples in this series. CSF in listeria meningitis frequently exhibits variable proteins, glucose,[1,12,13,17] and leucocyte content. Lymphocytic pleocytosis is a common feature,[1,17] and has been present in each of the five samples of CSF in this study. In a retrospective analysis of 54 cases[16] three were initially diagnosed as of viral origin on these criteria, with delay in proper antibiotic therapy as a result. Cases are known where erroneous initial diagnoses of tuberculous meningitis[16] and neurosarcoidosis[20] were made. Preliminary diagnoses of viral meningitis in case 1 and tuberculous meningitis in cases 1 and 4 were made in our group. However, all of our cases showed marked neutrophil leucocytosis in peripheral blood which could be a differentiating pointer. Aetiological diagnosis may not always be available even from CSF culture as four (out of 54) were sterile in one report.[16] Due to morphological pleomorphism listeria has been mistakenly dismissed as diphtheroids[1,29] and it appears Gram-negative rather than Gram-positive resembling *Haemophilus influenzae* in partially treated cases.

Serological tests for listeria infection are largely non-specific due to widespread cross reaction but purified *L. monocytogenes* surface glycoprotein (antigen 2) has been successfully used for diagnostic purposes by enzyme-linked immunosorbent assay. Serotype 4 contributed 74% of 127 human isolates between 1976–79.[21] Success with positive blood cultures in meningitic groups (15 of 17[16] and 9 of 18[1]) have been obtained but it was positive in only one of our four cases.

Listeria is an intracellular organism which survives and grows within macrophages protected and nurtured by many toxins/enzymes it produces.[14] Ideally the antimicrobial agent to treat listeria meningitis should have low blood-brain barrier threshold, be able to achieve good intracellular concentration and be bactericidal. None of the antibiotics used against listeria exhibits all these properties even though it is sensitive *in vitro* to many commonly used antibiotics. *In vitro* sensitivity results depend on methodology used[22] and may show inappropriate outcome in clinical experience. Ampicillin sensitivity has, as in three of our cases, been extensively reported[1,20,22,23] and is generally accepted as the drug of first choice[1,20,23,30] in a dose of 200–300 mg/kg body weight/day in six equally divided doses given intravenously every 4

hours for 14–21 days after defervescence.[24] However, resistance to ampicillin,[16] or only moderate susceptibility[8] have also been noted.

Ampicillin is only bacteriostatic against listeria[20] and its CSF penetration declines as meningeal inflammation subsides. *In vitro*, synergy of gentamicin with ampicillin was only demonstrable at a gentamicin concentration unlikely to be achieved in the CSF by parenteral therapy[23] and administration of aminoglycoside by lumbar puncture has produced only negligible ventricular concentrations.[25] Could the noted *in vitro* synergism[20,22,23] of ampicillin and gentamicin be an elusive concept?[26] Failure of ampicillin therapy in listeria meningitis, but success when switched over to chloramphenicol has been noted,[10,13,27] as happened in our case 4 in whom ampicillin did not reveal any improvement during 72 hours (although listeria was ampicillin sensitive) but made good recovery on chloramphenicol. Although bacteriostatic, chloramphenicol has good penetrating capacity into the CSF (independent of the degree of meningeal inflammation), in the brain substance and into the cell. Listeria is sensitive to it[1,8,20,22] as has been found in three of our cases. However, unfavourable experiences with chloramphenicol have been published.[23,28,30] Intravenous penicillin has been recommended as the drug of first choice by Hoeprich[24] but *in vitro* resistance,[8,20] as well as poor clinical results[1,14,31] have become frequent as was experienced in our third case.

Sensitivity records of listeria to cephalosporins (especially the third generation) have been disappointing. Resistance to latamoxef,[16,20,27] only moderate susceptibility,[27,32] or resistance[16,20] to cefotaxime, and resistance[16,18] to cefuroxime should dictate against using these drugs in bacterial meningitis in adults as monotherapy until the pathogen is characterized.

Treatment in a penicillin-allergic patient is a controversial problem. Trimethoprim-sulphamethoxazole, however, meets the criteria of choice[33] and *in vitro* sensitivity to this combination has been recorded.[8,20,34] Spitzer and colleagues[33] recorded five cures on this treatment and suggest this to be the drug of choice in patients allergic to penicillin. Recommended dose is 15 and 75 mg of trimethoprim and sulphamethoxazole respectively per kg body weight per day given intravenously in three equally divided doses 8-hourly for 14–21 days after defervescence.[24]

Overall mortality rate in listeria infection is around 30%[1,14] which is not surprising given the extremes of ages and the background of ill-health in those affected. Adult meningitis cases seem to score rather better cure rates without[13,17] or with[33] associated diseases. Amongst the poor prognostic indicators convulsion[16] and CSF glucose concentration below 1.7 mmol/l[1,16] seem to be useful, but two of our three patients with low levels were cured.

A heightened degree of alertness is required to diagnose CNS infection due to listeria. Lymphocytic meningitis of rapid onset (particularly if impaired consciousness level is associated) should not be readily discounted as benign viral meningitis even though the victim is a previously healthy adult. Cephalosporins are not recommended in treatment of listeria meningitis. Ampicillin is the drug of choice. In penicillin-allergic individuals trimethoprim-sulphamethoxazole or perhaps chloramphenicol could be used. The drug should be started promptly, intravenously, in appropriate dose and for appropriate duration to achieve the best outcome.

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