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58. LISTERIOSIS

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MATERNAL ASPECTS

Definition

Listeriosis, a disease caused by *Listeria monocytogenes*, presents in a variety of fashions. In the adult, it is a rare cause of meningitis, septicemia, endocarditis, peritonitis, and focal abscess; however, its greatest clinical significance is in the area of perinatal infection. It has been shown to cause abortion, stillbirth, and "granulomatosis infantiseptica," which is a life-threatening septic illness. *Listeria monocytogenes* is the third most common cause of neonatal bacterial meningitis after *E. coli* and *S. agalactiae*. In European countries where *L. monocytogenes* is reported to a central agency, the organism is responsible for 1–7% of perinatal mortality.[1]

Etiology

Listeria monocytogenes is a small uniformly staining gram-positive microaerophilic bacillus that does not produce either capsules or spores. An important clue to identification is its characteristic tumbling motility seen at room temperature but not at 37°C. The organism is often confused with diptheroids or streptococci, which may be responsible for the underreporting of *L. monocytogenes*. Weakly hemolytic gram-positive bacilli are presumed to be *Listeria* when they exhibit the characteristic motility at 20 to 25°, reduce 2,3,5-triphenyltetrazolium chloride, and display characteristic animal pathogenicity such as the Anton test (keratoconjunctivitis, which develops in rabbits or guinea pigs 3 to 5 days after inoculation of the organism into the conjunctival sac). At least seven serotypes have been defined on the basis of 0 and 4 antigens, with types 4B, 1B, and 1A being responsible for over 90% of cases worldwide.

Pathogenesis and Pathology

More work is necessary in this area; for example, the incubation period is unknown in most cases. The GI tract is presumed to be the usual portal of entry for most forms of the disease, but the time interval for septicemia to be manifested and how the organism gains access to the meningeal cavity are also unknown.

The basic lesion is miliary granulomatosis with focal necrosis or suppuration in involved tissues. Pinhead white areas, which are clearly visible in the liver, adrenals, and lungs but less apparent in kidney, GI tract, and spleen, are distributed throughout the viscera. Under the microscope, these areas show well-circumscribed nodules in otherwise normal tissue or diffuse focal necrosis. What is termed "meningitis" may be more appropriately called "meningoencephalitis," since disseminated focal necrosis with mononuclear and glial cell reaction can be found in the brain in many cases.

Epidemiology

The organism has been identified worldwide except Antarctica and has been isolated from over 50 species of animals including mammals, fowl, and fish. In addition, it has been isolated from water, mud, sewage, and silage. Because the organism is remarkably resistent to ultraviolet light and sunlight and is capable of withstanding repeated freezes and thaws, it has been known to survive in contaminated environmental sites for months.[2] A carrier state has been identified in healthy humans and animals; for example, it may be isolated in from 1 to 60% of human feces. Vaginal and cervical carriage have been reported at rates of less than 1%.

Although the disease is underdiagnosed and underreported, the mode of transmission in most cases appears to be obscure. Direct contact with infected material has been implicated in the spread of the disease among poultry workers and veterinary surgeons. At least one case of human-to-human transmission has been reported; a pregnant physician who treated a patient with listeriosis shortly afterward gave birth prematurely to an infected stillborn infant. A recent report strongly suggests that transmission by food may play a role in epidemics.[3] Manure-contaminated cabbage that had been cold stored was used for prepared coleslaw; *L. monocytogenes* serotype 4B was isolated in a statistically significant amount from the patients who had eaten the coleslaw but not from controls. Milk and other food had previously been implicated in transmission, but these are not as carefully documented.

Venereal spread has been known for animals and man, and this may be a route of transmission for in-utero infections by the ascending route; certainly, vaginal or cervical carriage appears to be the way in which the late-onset neonatal meningitis is transmitted. Listeriosis has a

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predilection for those under 1 and over 55. Host resistance factors clearly play a role. Certain malignancies, particularly of the reticuloendothelial system, chronic debilitating diseases such as tuberculosis and diabetes, and the immunocompromised state increase the risk for infection. Pregnancy also is associated with the same greater risk of infection. Healthy individuals have been known to become victims of the disease; stress may play a role in altering host defenses. In most reported cases in adults, neither the source of infection nor the route of transmission is clear.

Clinical Manifestations

In most pregnant women whose offspring develop listeriosis, there is a brief flulike illness with nonspecific signs and symptoms such as fever, chills, generalized myalgia, pharyngitis, diarrhea, and occasionally urinary tract symptoms. Positive blood culture for *Listeria* can be obtained during this stage. The illness may be present at any time during pregnancy but often triggers premature labor with intact membranes.

A few patients develop significant *Listeria* septicemia with high spiking fevers associated with nonspecific findings such as fatigue, malaise, and some type of abdominal complaint (nausea, vomiting, pain, and diarrhea). Two cases of adult respiratory distress syndrome (ARDS) (one fatal) have been reported[4]; the index of suspicion for *L. monocytogenes* should be high if ARDS occurs in a pregnant patient. *Listeria* endocarditis has been reported in a pregnant diabetic; one pregnant patient with tuberculosis developed a fatal *Listeria* meningitis. If listeriosis in pregnancy remains undiagnosed for over a week, deceased fetal movements and stillbirth will probably occur. The disease has also been associated with signs of fetal distress by biophysical and biochemical monitoring.[5] Most mothers become afebrile with delivery even without treatment, but recurrences 10 to 20 days post-partum have been reported and interpreted as reinfections from contact with the contaminated placenta. If the disease occurs in the first or second trimester, an infected abortion would be expected. *Listeria* certainly should be considered as the differential diagnosis of infected abortions because it is probably more common than realized.

Laboratory findings include nonspecific leukocytosis of variable degree, but monocytosis is uncommon. Blood cultures for *L. monocytogenes* are positive in most cases, but the organism grows slowly. Occasionally the organism can be cultured from the amniotic fluid or the cervical secretions in infected individuals.

Differential Diagnosis

The differential diagnosis in pregnancy is obviously difficult and includes all fevers of unknown etiology. Listeriosis is often not suspected because of the vague nonspecific influenzalike symptoms even if the patient seeks medical attention.

Both the endocarditis and meningitis resemble the other bacterial forms of the disease and are confirmed only by culture. Serodiagnosis for agglutinins is not helpful because of the so-called "naturally occurring antibodies," which reflect the known antigenic relationship between *Staphylococcus* and several *Listeria* serotypes. Recent isolation of the main immunologic antigen of *L. monocytogenes* may make serologic tests more useful in the future.[6]

Treatment

Listeria monocytogenes are susceptible to several antibiotics in vitro including penicillin G, erythromycin, rifampin, streptomycin, gentamycin, tobramycin, and tetracycline; however, tolerance, is characteristically seen with the first four antibiotics listed. For this reason, combination therapy is used for maximal listericidal effects. One proposed regimen is penicillin G, 240,000 to 320,000 units/kg per day given IV in six equally divided doses q 4 h, plus tobramycin, 5 to 6 mg/kg per day IV divided into three equal portions every 8 h. An alternative regimen, which offers no advantage, uses ampillicin and gentamicin at similar doses. Erythromycin may be substituted in the pregnant patient who is allergic to penicillin and its derivatives. Therapy should be continued for at least 2 to 3 weeks. Fetal survival rates of 80% have been reported when prompt diagnosis was made in the mother and appropriate antibiotic therapy instituted.[7]

Trimethoprim–sulfamethoxazole has been proposed as a bactericidal drug that can be given orally in patients allergic to penicillin at a dose of 1200 mg (three tablets) every 8 h for 2–3 weeks. This drug is contradicted in late pregnancy and during lactation because it interferes with bilirubin metabolism. It is teratogenic in high doses in rodents because it interferes with folic acid metabolism. Although the drug has been used in 35 cases in early pregnancy without resultant congenital abnormalities, it probably should be avoided completely in pregnancy.[8]

Prevention

Since the epidemiologic source and mode of transmission are unknown for most patients, prevention is difficult. All pregnant patients should be encouraged to use good personal hygiene and to avoid handling livestock and potentially contaminated animals. In addition, raw milk, rare meat, and fresh vegetables that are stored at cold temperatures for prolonged periods of time (cabbage and some raw vegetables) should be avoided. A high index of suspicion in pregnant patients with febrile illnesses and utilization of cultures for *Listeria* would help prevent the disease in the newborn.

FETAL ASPECTS

Pathogenesis and Pathology

Like *Strep. agalactiae* infections, *L. monocytogenes* in the fetus presents both an early- and late-onset disease. Intrauterine infection may occur early in pregnancy and lead to spontaneous abortion. The infant may be affected either through the hematogenous route when maternal illness exists or through the ascending route from the colonized vagina with subsequent amniotic infection through intact membranes. The fetus then becomes infected by ingestion and/or aspiration of contaminated amniotic fluid. Since the heaviest concentration of neonatal disease is in the gut and lungs, this mechanism plays a significant role. The placenta may show the characteristic miliary abscesses both on the fetal surface and in the intervillous spaces as well as evidence of chorioamnionitis along the membrane surface and within the cord.

In the late-onset form of disease with delivery through a contaminated birth canal, meningitis develops with onset after the fifth day of life.

Clinical Manifestations

If the infection is significant and unrecognized in utero, a stillbirth results. With early-onset disease, the infant may be born prematurely and manifest signs of fetal distress. The amniotic fluid is often meconium stained; meconium cultures are positive for *L. monocytogenes*. These infants often manifest early signs of respiratory distress and have coarse mottling on chest X ray; in addition, they often have microabscesses in the gut, which cause mucous diarrhea, CNS involvement with seizures, and a discrete roseolar pustular eruption of the skin and posterior pharynx. Most of these infants will have hepatosplenomegaly and other signs of early sepsis and appear severely asphyxiated at the time of birth. If the infant does not have *granulomatosis infantiseptica* at birth but instead becomes infected by aspiration of the thick meconium, survival is improved by vigorous tracheal suction.

The mortality from granulomatosis infantaseptica is quite high in most series, with fatality rates of 27% to 60% among liveborn infants. Long-range sequelae include pulmonary dysplasia secondary to prolonged respiratory assistance and secondary infections with pathogens such as cytomegalic virus; early recognition of *L. monocytogenes* infection has been life saving in some circumstances. The diagnosis can be made by isolation of the organisms from the amniotic fluid, placenta, neonatal ear, gastric aspirate, and, particularly, from meconium. Infants with the late-onset disorder usually appear normal at birth but subsequently develop fever, irritability, and poor feeding associated with bulging fontanelles. A positive cerebrospinal fluid establishes the diagnosis of meningitis. Maternal genital carriage is variable in duration, but endometrial and blood cultures should be obtained. Most of the cases of neonatal listeriosis are associated with intact membranes.

Laboratory diagnosis (other than cultures of the infected infant) is not always helpful. Either leukocytosis (above 30,000/mm^3) or leukopenia with a left shift may be present. There has been some suggestion that infants born with congenital listeriosis have elevated fibrinogen levels; values above 340 mg/100 ml have been seen in 80%.[9]

Treatment

As with the adult patient, treatment with a combination of antibiotics seems to be most efficacious in killing the organism. Ampicillin is often used in the infant because of its low toxicity and because it get into the cerebospinal fluid well. The recommended dosage varies between 100 and 200mg/kg in divided doses IV every 4 h coupled with gentamicin, 4 mg/kg per day in three divided doses IV or tobramycin at 5–6 mg/kg per day. Even if the infection is eradicated in the infant, victims may ultimately succumb to complications of prematurity (intraventricular hemorrhage or hyaline membrane disease) or may suffer the delayed sequelae such as intracranial hemorrhage or bronchopulmonary dysplasia. Hydrocephalus with seizures and chronic cytomegalic virus infection have also been reported in survivors. At least one-third of survivors are reported to be neurologically and physiologically normal.[10]

Combination therapy is continued for 10 to 14 days followed by ampicillin or amoxicillin alone for a full therapeutic course of 21 days to avoid secondary meningitis; the latter has been reported in some neonates with early-onset disease who were treated for less than 2 weeks.

Prevention

Nothing can be done to prevent the infection in the fetus unless maternal disease or colonization is recognized earlier and appropriate therapy instituted.

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