Listeriosis

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Summary

The incidence, clinical picture, natural history, epidemiology and sequelae of perinatal listeriosis are discussed along with treatment and diagnosis.

Introduction

Listeriosis is an uncommon disease in Britain but is probably not sufficiently recognized. It is due to an opportunist pathogen *Listeria monocytogenes* and occurs in three main forms, meningitis, perinatal listeriosis and an anginal form. Much rarer forms include septicaemia with isolated organ involvement and abscess formation. It usually attacks the old, the very young, the pregnant and people with impaired defences. The epidemiology and mode of spread apart from mother to fetus is obscure. The perinatal disease is distinctly rare in Britain and carries a high mortality for the child but the mother usually has a very mild illness.

Incidence

Between 1972 and 1975 twenty-four neonatal cases of listeriosis were reported from Britain and the Irish Republic, all with meningitis. Nine recovered and in six the outcome was not stated. This is a mortality rate of 40-64%. Other series such as that of Sepp and Roy (1963) in Canada have reached as high as 91%.

Perinatal listeriosis was first described as a cause of abortion and neonatal mortality in Halle, East Germany, by Reiss, Potel and Krebs (1951). Gray and Killinger (1966) graphically described the conditions under which the German doctors were working—a bombed-out hospital in a ruined city with only one power point working in the laboratory. It is a great credit to them that the disease was recognized as a separate entity. Their short report describes fifteen cases, and their clinical picture and diagnostic advice have not really been improved upon. They called the condition 'granulomatosis infantiseptica' as their cases were characterized by generalized tiny granulomata in many organs including the placenta. The disease has since been

studied many times in Germany where it has caused minor outbreaks in Bremen, again in Halle and in other parts. An outbreak has also been described by Becroft *et al.* (1971) in New Zealand involving thirteen cases with a mortality of 54%. Seeliger, Emmerling and Emmerling (1969) recorded 2004 human cases of all forms of listeriosis and 3173 animal cases in the whole of Germany between 1950 and 1966. *Listeria* is an important animal pathogen and, indeed, was first isolated from rabbits and guinea-pigs in Cambridge by Murray, Webb and Swann (1926).

In Germany, perinatal listeriosis is the commonest form of the human disease, 58.1% of Seeliger *et al.* (1969) series of 752 bacteriologically-proved cases were of this form counting mother and child as one case, 37.2% were neurological, which proportion would have been greatly increased if neonatal meningitis had not been classed as perinatal listeriosis and only 4.7% of these cases were other forms of the disease. Conversely, in America, the neurological disease is commoner. A series of 731 cases between 1937 and 1966 described by Killinger and Schubert (1966) included only 13% affecting pregnant women and newborn infants. The neurological form is commoner in Britain. The disease as a whole is increasing in frequency in Germany, Holland, France and the U.S.A., possibly owing to better diagnosis and, according to Seeliger *et al.* (1969), it is commoner in Germany than anthrax, leptospirosis, tularaemia and puerperal fever and not much rarer than Q fever, poliomyelitis, tetanus and botulism. It has been described from many other countries including Denmark, Iceland and Czechoslovakia.

The sheep is the commonest infected animal in Germany and both human and animal cases show peaks of incidence but these alternate rather than coincide. Great Britain has a low rate of animal infection, mostly in sheep and cattle but also in chickens. Seasonal peaks occur in late winter and early spring possibly associated with the feeding of silage which may harbour the organism.

Clinical picture

Most British cases of perinatal listeriosis have been fatal for the infant until recently. The clinical picture can best be described by referring to Gray and Killinger's (1966) composite picture drawn from many cases and publications and which fits well with the two cases in this author's own experience and another recently described by Robson and Peel (1976). There are no clinical signs which distinguish *Listeria* infection from common disorders of pregnancy such as pyelitis. The mother is usually not seriously ill and many cannot remember any symptoms suggesting infection. Others mention influenza-like symptoms or diarrhoea a few days or weeks before parturition. Generally speaking, some time in the second half of pregnancy there are sudden chills accompanied by pyrexia, sore throat, headache, mild dizziness, pains in the back, discoloured urine and perhaps loose stools. These symptoms vanish after 2 or 3 days only to recur, in some instances, after another few days. Soon after the first pyrexia fetal movements become less vigorous and premature delivery or still-birth follows within 1 week. The amniotic fluid is murky and discoloured but not malodorous and the placenta contains small grey necrotic foci. The mother becomes asymptomatic and the puerperium continues without complication although the organism can be isolated from the birth canal for a few days or even weeks.

In contrast, the infant is either still-born or, if alive, may be affected in two ways. Either he is acutely ill, especially if premature as is usual, or apparently well only to develop meningitis later. If acutely ill, death may occur within minutes or hours and survival without treatment beyond 3 days is exceptional. Ante-mortem diagnosis is clinically difficult as there are no signs to distinguish this condition from any other severe infection. The respiratory and neurological systems are severely affected. Dyspnoea, cyanosis, soft whimpering or grunting are very prominent symptoms. Low body temperature, vomiting, early passage of meconium or mucus-like stools occur and a red papular rash may appear over all or part of the body. Purulent discharge from the eyes or nose may appear and if the child survives long enough suppurative meningitis supervenes leading to hydrocephalus or mental deficiency if the child survives.

If apparently well at birth, meningitis appears after a few days, weeks or even months of extra-uterine life. This type of the illness is much commoner than perinatal septicaemia of which only six British cases can be traced, including the author's own, where meningitis was not a feature. Four came to post-mortem and the two survivors were probably treated before the meningitis had time to develop.

This meningitis has nothing to distinguish it clinically from any other bacterial meningitis.

Natural history

The natural history of the disease has been built up by correlating placental studies with the clinical history of mother and child. Sarrut and Alison (1967) described three possible types of infection.

(1) Transplacental from the mother's blood producing widespread lesions in the child and placenta but sparing the fetal lungs unless these are the site of a bronchopneumonia due to inspiration of liquor amnii infected via the fetal urine. The liquor, however, need not be infected. The maternal serology should be positive and lochial cultures may be positive or negative.

(2) A simple transmembranous infection of the liquor amnii arising from listerial endometritis or by spread from cervicitis. In this case lesions are absent from the placenta and there are abundant organisms in the liquor amnii. The lesions in the child are mostly in the lungs, digestive tract, skin and eyes as a result of inhalation, ingestion and contact with the infected liquor.

A subdivision of this type of infection can account for the children born apparently healthy but who develop meningitis after a few days, weeks or even months of life. The infection of the cervix may never cross the membranes to infect the liquor but the child, during birth, can inhale or be smeared with *Listeria* from the birth canal. This could lead to a localized infection in the ear or nasopharynx eventually producing meningitis via the middle ear or cribriform plate. The maternal serology is usually negative and lochial culture positive.

(3) A localized infection of the placenta originating from an endometritis. This type has abscesses in the placenta, sometimes isolated sometimes associated with infected liquor. While the organisms remain localized there is no manifestation in either mother or infant. The maternal serology is negative but the lochial culture could be positive. If the organisms diffuse for any reason, the picture of type I supervenes, the mother has a febrile episode and the child is affected.

Source of maternal infection

The source of infection of the pregnant woman is obscure. Feeding experiments with animals suggest that the oral route is the most likely avenue of infection and many East German human cases were in women drinking unpasteurized milk. Potel (1953) has isolated *Listeria* from a cow whose milk had been drunk by a woman who aborted owing to *Listeria* infection of the same serotype as that infecting the cow. This is the only case so far described directly linking listeriosis to raw milk. The

organism can be isolated from the faeces of at least 1% of healthy Danes at any time according to Bojsen-Møller (1972) but the duration of carriage is short, lasting only a few days or at most a few weeks. An incidence of 0.6% faecal carriage was found in Swansea residents by Kwantes and Isaac (1971). These last workers also isolated *L. monocytogenes* from twenty of thirty-five chickens sold for the table. Seeliger *et al.* (1965) were able to grow it from compost and garden soil from the house of an infected woman and from the stools of both the patient and her husband. The same workers also described a dog secreting *Listeria* whose owner, a lady doctor, had aborted and had a fairly high level of antibodies to *Listeria*, 1 : 320. On removal of the dog her antibody level fell to the 'normal' of 1 : 80. Domestic and other animals, at least fifty-five species have been listed by Gray (1963), are known to harbour *Listeria* and Bojsen-Møller (1972) lays great stress on contact with animals or animal products as a source of oral infection. He found a higher incidence of faecal carriers among slaughter-house workers than in people in other employment.

It appears likely, therefore, that the organisms can be swallowed either with raw milk, meat or soil-contaminated vegetables or during occupational contact with meat or animals and is carried in the intestine for a short period during which it is capable of infecting the pregnant woman. This may be associated with a bout of diarrhoea from some other cause, or perhaps a urinary infection due to *Listeria* from the bowel, each possibly giving access to the blood stream.

Transperineal spread from anus to vulva could lead to colonization of the vagina, cervicitis and transmembranous infection. The venereal route is also a possibility. Toaff, Krochik and Rabinovitz (1962) have demonstrated *Listeria* in the semen of the husbands of three habitual aborters. Two of the wives also had genital listeriosis. On treating both partners, successful pregnancies ensued.

Sequelae of infection

Rappaport *et al.* (1960) in Israel incriminated persisting listerial infection of the birth canal as a cause of recurring abortion and claimed to have cured this condition by antibiotic therapy directed against the organism. There are few supporting publications. Dungal (1961) in Iceland described a similar incident in one case and Oehlschlager (1960) another less well proved case. Rabau and David (1963) in Israel failed to find evidence to support Rappaport *et al.* and neither could Macnaughton (1962), Robertson (1966) or Scott and Henderson (1968) in Britain, or Lawler *et al.* (1964) or Quarles and Pittman (1966) in America. Potel and Alex

(1956) with great experience of the disease had previously rejected the idea.

Mental retardation in surviving children as a result of permanent brain damage has been suggested as a possibility by Lang (1955). This was based on serological studies in mentally retarded children. Forty-three out of eighty-seven children with retardation of no established aetiology had significant titres against *Listeria* while only five of fifty in which the aetiology was known had similar levels. Serology in this disease is of doubtful accuracy at present and this work was not confirmed in another study on 200 mentally retarded children by Miller (quoted by Gray and Killinger, 1966). The possibility, however, remains intriguing.

Treatment

Treatment falls into two divisions, that of the pregnant woman and that of the affected child. The first requirement in each instance is a high degree of suspicion on the part of obstetrician, paediatrician and microbiologist as the clinical manifestations have nothing diagnostic and colonies of *Listeria* can easily be disregarded in the laboratory as 'diphtheroids' or contaminants.

Diagnosis of the pregnant woman depends upon blood culture and/or cervical culture and these samples should be taken from any woman giving a suspicious history. In the author's experience, the organism grows readily from blood culture and this identity can be suspected in 24 to 48 hr. A motile, Gram-positive bacillus of 'diphtheroid morphology' producing small weakly β -haemolytic colonies on a blood agar plate should be treated as *L. monocytogenes* until proved otherwise and appropriate antibiotic therapy commenced. Only a handful of cases, the author found ten, thus diagnosed and treated have been recorded in the literature and as the antibiotics used varied so greatly little can be gleaned except that tetracycline given alone is probably not adequate to clear the organism from the genital tract. Gentamicin and ampicillin used in combination is logical and the author's treatment of choice. The organism is usually susceptible to both drugs and they penetrate into the sites where it must be killed. Garrod, Lambert and O'Grady (1973) give the minimum inhibitory concentration of gentamicin for most strains of *L. monocytogenes* as 0.12 $\mu\text{g/ml}$ and of ampicillin as 0.5 $\mu\text{g/ml}$. The aminoglycosides produce fetal blood levels about one-third of the maternal and gentamicin penetrates into the cerebrospinal fluid in low concentrations which are, however, adequate for this very susceptible species. Marsden and Hyde (1970) record cerebrospinal fluid levels of from 0.6 to 1.25 $\mu\text{g/ml}$ in children on intramuscular therapy alone. They do not, however, yield high amniotic fluid levels. In the author's own

case maternal gentamicin blood levels of 3 µg/ml, which is well below the ototoxic level, presumably yielded fetal levels of 1 µg/ml while the particular strain of organism was killed at a concentration of 0.15 µg/ml. Ampicillin, conversely, produces much lower fetal blood levels, being excreted in the fetal urine, thus, however, yielding very high amniotic fluid levels. In the author's case the bactericidal level of ampicillin was greater than 8.0 µg/ml, surprisingly higher than the static level of 0.06 µg/ml, but the combined therapy yielded a live, healthy infant with no toxic effects on either mother or child. Treatment of the mother should be continued for at least a fortnight or until delivery, whichever is sooner. Treatment of the mother will probably then become unnecessary but the child must be carefully watched for signs of infection, especially meningitis, for at least 3 months. In the author's case the child did not receive any antibiotics after birth and has remained well.

Diagnosis of the affected infant is the province of the paediatrician. Difficult breathing is perhaps the commonest manifestation and this seems to indicate that the diagnosis should be considered in all cases of respiratory distress. Blood or CSF culture is diagnostic but meconium swabs from the child's surfaces, eyes, umbilicus, etc. will yield the organism if the liquor amnii has been infected. Should the child have been bathed, an ear swab may still yield *Listeria*. These swabs are easily obtained even if venepuncture or lumbar puncture prove difficult.

Culture on blood agar overnight at 37°C yields typical colonies and a presumptive diagnosis can be made. Treatment is gentamicin and ampicillin controlled by blood levels, and full supportive therapy including oxygen which it may prove difficult to withdraw.

The child born apparently well from a known *Listeria*-infected mother must be carefully swabbed for culture and, if no infection is found, carefully watched for the development of meningitis or respiratory infection. It may be advisable to carry out lumbar puncture as a screening measure soon after birth and certainly on the slightest suspicion of clinical disease. The child's mental development should also be carefully followed so that special schooling can be arranged if necessary.

Serology

Serology has been mentioned several times in this paper but it must be stressed that at present findings are unreliable and until better methods are devised must be interpreted with care. Neter, Anzai and Gorzynski (1960) point out that cross agglutination with staphylococci, streptococci and corynebacteria occur, and sera must be absorbed with *Staphylococcus aureus* before testing for *Listeria* agglutinins.

Many authors have omitted to do this. At least four serological types of *L. monocytogenes* exist.

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