LISTERIOSIS: A CAUSE OF PERINATAL INFECTION

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Although listeriosis is presently a very well known cause of neonatal infection, very little is done to prevent it during pregnancy and the incidence has remained stable during the last ten years in Western Europe (West Germany and France) as well as in the United Kingdom, where the disease still seems to be very rare (Relier, 1979; Seelinger and Finger, 1976).

Several extensive reviews have been published and the aim of this paper is to discuss recent data concerning the epidemiology during pregnancy and the prognosis in the newborn.

EPIDEMIOLOGY

The mode of acquisition of *Listeria monocytogenes* from the environment remains obscure; the majority of human infections cannot be explained by transmission from animals and the high frequency of listeria antibodies in man suggests that listeriosis in animals and the human can occur independently. Transplacental infection and direct acquisition from the vaginal canal are thought to cause perinatal infections, but the source of infection of the mother is not always clearly identified.

Recently, Schlech *et al.* (1983) reported a large outbreak of both adult (7 cases) and perinatal infection (34 cases) due to *L. monocytogenes* serotype 4b, where contamined coleslaw was identified as the probable vehicle of transmission. This product was obtained from a farm known to have had cases of ovine listeriosis. Cabbage was grown in fields fertilized with both composted and raw manure from the flock of sheep. These findings suggest that the source of listeria infection could be contamined food, with indirect transmission of listeriosis from an animal reservoir to human beings, which has been previously assumed (Blenden and Szatakowicz, 1967) but never proved. These authors describe the full epidemiological cycle.

This article adds important data to our knowledge of the epidemiology of listeriosis in urban communities. It confirms the data of Ho *et al.* (1981) suggesting that consumption of lettuce or other raw vegetables may be linked to listeriosis in hospitalized immunosuppressed patients and strengthens the study of Fabiani *et al.* (1976) who found that among 275 persons of miscellaneous age and origin the rate of healthy carriage was 5%. In 1972, Kamperlmacher and Van Noorle Jansen (1972) found listeria in 12% of healthy workers and 44% of healthy pregnant women. Clearly, pregnancy is an important risk factor, but it cannot explain the pathogenesis since not all pregnant women who are fecal carriers will have invasive listeriosis. The amount of contaminated food ingested might be an important factor, but this is very difficult to assess.

In conclusion, the role of raw vegetables in sporadic and epidemic listeriosis appears to be important and it might be reasonable to suggest that pregnant women should not consume too much raw vegetable from unknown origins.

Clin. Exp. Obst. Gyn. - ISSN: 0390-6663
XIII, n. 3-4, 1986

CLINICAL MANIFESTATIONS AND PROGNOSIS

The clinical features of listeriosis during pregnancy and in the newborn, during the perinatal period, have been previously described (Relier, 1979; Seeliger and Finger, 1976). From our experience at "Port Royal Hospital" during the last 15 years, the improved prognosis is mainly due to earlier diagnosis during pregnancy and in the neonatal period. From January 1971 to January 1983 (12 years), 110 cases were admitted to our neonatal intensive care unit: 25 died (22.7%) but the highest incidence of mortality was in those of below 32 weeks gestational age (19/45 i.e. 42%); 4/37 between 33 and 36 weeks gestation (10%) died and only 2/26 between 37 and 41 weeks gestation (7.6%) died. Causes of death in the low birth weight infants were mainly intraventricular and intracranial haemorrhage, and meningo-encephalitis associated with lung disease. 19/110 had meningitis. Clinical and biological features were characteristic in 12 cases; the gestational age was between 26 and 31 weeks and maternal fever as always present. All newborns had leucocytosis above 30,000 per µl and respiratory distress syndrome with an abnormal lung picture. CSF showed high protein up to 6 g/l or more and low glucose (less than 1 mmol/l). *Listeria monocytogenes* was isolated from CSF in 10 of 12 infants but no listeria was found in CSF after 24 hours of antibiotic therapy. However, biological abnormalities lasted more than a month (protein above 4 g/l, neutrophils, then lymphocytes, 150 or more per µl). All the newborns who died had seizures before death. Larroche (1977) suggested that the term meningo-encephalitis would be more appropriate than meningitis to the autopsy findings, since in many cases disseminated foci of necrosis with mononuclear and glial cell reaction are found in the brain. The outcome of listeria meningo-encephalitis is poor: out of the 12 with meningo-encephalitis, only 6 survived: 2 were lost for follow-up, 1 was completely normal, 2 had slight retardation, 1 had a valve for hydrocephalus at 2 months of age but was considered normal at 2 years of age.

THERAPY

L. monocytogenes is still very sensitive to antibiotics. However, most authors consider that the dangerous nature of the infection, especially in neonates, fully justifies treating listeriosis with multiple antibiotics. The most rapid and complete killing will be obtained by combination therapy: a beta-lactam plus an aminoglycoside is often sufficient.

PREVENTION

Obviously the best policy would be to prevent maternal listeriosis which would prevent both fetal listeriosis and premature delivery. Perhaps every febrile pregnant woman should be given antibiotics. Other measures for prevention of infection in women exposed to the risk of contamination or even to every pregnant woman living in countries with endemic listeriosis could include personal hygiene and dietary restrictions, avoiding ingestion of raw milk and raw vegetables from unknown sources.

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CONGENITAL MALARIA

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Hippocrates recognised the periodicity of certain intermittent fevers and classified them into quotidian, tertian and quartan types. In the middle ages these fevers became known as malaqua (bad water) and malaria (bad air) because of their known association with the miasma arising from marshy areas. However the cause of malaria remained a mystery until 1880 when Alphonse Laveran described the parasite in the peripheral blood films of patients suffering from this disease. In 1894 Ronald Ross discovered the malarial parasite in the salivary glands of the female anopheline mosquito. Thus the horizontal transmission of malaria from the mosquito to humans and back again was described. Subsequently other modes of transmission were described for example blood transfusion, accidental inoculation, inoculation amongst heroin users and finally vertical transmission from the pregnant mother across the placenta to the fetus.

IN ENDEMIC AREAS

Despite attempts at the control of the horizontal transmission of malaria it remains the most important human parasitic disease. Other modes of transmission have not been thought to play an epidemiologically important role. Vertical transmission is thought to be rare (0.03%, Covell 1950) in endemic areas despite the greater prevalence and density of malaria among pregnant than non pregnant women Gilles *et al.*, 1969; MacGregor and Avery, 1974; Reinhardt, 1978; Bray and An-

Clin. Exp. Obst. Gyn. - ISSN: 0390-6663
XIII, n. 3-4, 1986

derson, 1979). Three factors might account for this apparent rarity – the placental barrier, maternal immune mechanisms and factors in the newborn infant.

In endemic areas up to 80% of unselected pregnant mothers have infected placentae (Blacklock and Gordon, 1925; Schwetz and Peel, 1935; Garnham, 1938; Logie and McGregory, 1970; Reinhardt *et al.*, 1978). The placenta is a preferential site of reproduction and growth for the malarial parasite. Asexual schizogony forms may be demonstrated in enormous numbers in the intervillus spaces despite a maternal peripheral blood film which may be free of parasites (Clark, 1915; Garnham, 1938; Reinhardt *et al.*, 1978).

The placenta is a relative and not an absolute barrier. Even transplacental transmission of maternal erythrocytes does occur (Zarou *et al.*, 1964). Transplacental transmission rates, as defined by the finding of malarial parasites in thick films of cord blood from unselected births in endemic areas, have usually been quoted as 2-9.7% (Lombart, 1932; Hentsch, 1955) but more recently as 44% (Atkins, 1957), greater than 30% (Okeke, 1970) and 21.7% (Reinhardt, 1978). These figures are an understimate of the true transplacental transmission rate because the parasite density in cord blood is light and easily missed by the relatively crude screening method of peripheral blood film examination (Hindi and Azimi, 1980).

Maternal immunoglobulins passively acquired before birth or during breast feeding offer the newborn infant temporary protection. There is rapid clearance from the blood stream of parasites coated with maternal immunoglobulins (Reinhardt, 1978). This clearance mechanism is supported by the finding of higher transplacental transmission rates in the cord blood than in the peripheral blood of the same newborn infants (Lombart, 1932). Antibody may circumscribe the malarial parasites but does not necessarily eradicate them for there is evidence that malaria may be precipitated by immunosuppression in those who have had no overt signs of the disease for many years (Ashford *et al.*, 1980).

In newborn infants fetal haemoglobin has a retardant effect on the malarial parasite (Hendrickse *et al.*, 1971; Pasvol *et al.*, 1976). Added to this inhibitory effect is the relative deficiency of amino-benzoic acid caused by the solely milk diet of the newborn (Maegraith *et al.*, 1952).

Should the passively acquired immunity and the newborn infant's own defences be inadequate to eradicate the transmitted parasites and only able to suppress them, the parasites could enter a latent phase. Even in non-immune individuals originating from non endemic areas, congenital malaria rarely presents before three to four weeks of age. In endemic areas a more prolonged latent phase would occur in those infants with a high degree of passively acquired immunity. Such cases presenting after several weeks or months could be classified erroneously as acquired malaria.

Given the increased prevalence and density of parasitaemia during pregnancy in endemic areas and the more recently defined higher transplacental transmission rates, it is possible that vertical transmission is a major mode of acquisition of malaria in early infancy. The recent increase in reports of congenital malaria in South

East Asian immigrants in the United States of America (13 cases from 1966 to 1979 and 13 cases in the eighteen months from January 1980 to July 1981) tends to support the hypothesis that vertical transmission of malaria is not rare in endemic areas. There is epidemiological evidence (Bray and Anderson, 1979) to support this hypothesis in that the peak prevalence and density of malarial parasitaemia in young infants occurs some months after the rainy season. This might be expected because transplacentally acquired immunity in infants born in the rainy season would be at its nadir at this time.

Should vertical transmisison prove to be a major mode of acquisition of malaria, the treatment of selected pregnant mothers and their newborn infants in some endemic areas may offer some hope for greater success in the control of this disease in early infancy.

IN NON ENDEMIC AREAS

Due to the ease of travel to endemic areas there has been an increased exposure of United Kingdom residents to malaria (Bruce-Chwatt, 1982). The increased exposure together with failure of such travellers to take adequate prophylactic measures has led to 1576 cases of malaria (*P. virax* 70.4%, *P. falciparum* 23.4%, *P. malariae* 0.8%, *P. ovale* 1.3%; mixed species 1.1%; species unspecified 2.7%) being reported to the Malaria Reference Laboratory in the United Kingdom in 1981.

A history of maternal exposure to malaria and subsequent infection may be obvious. However, this is not necessarily the case as exposure may not involve travel to an endemic area e.g. airport personnel (Saliou *et al.*, 1978), drug addicts (Keitel *et al.*, 1956; Friedman *et al.*, 1973), post transfusion or relapse as a consequence of infection months or years before (Harvey *et al.*, 1969; Bruce-Chwatt, 1982). Moreover malarial parasitaemia may be asymptomatic (Keitel *et al.*, 1956; Harvey *et al.*, 1969; CDC: malaria surveillance, 1974) or present as a pyrexia of unknown origin depending on the immune status of the mother.

Since 1907, nine cases of congenital malaria (5 *P. vivax*, 3 *P. falciparum*, 1 *P. ovale*) have been reported in the literature in the United Kingdom (Moffat, 1907; Jones and Brown, 1924; Tanner and Hewlett, 1935; Gammie, 1944; Dimson, 1954; Jenkins, 1957; Dodge, 1971; Bradbury, 1977; Meerstadt and Wright, unpublished data). 2 of these cases occurred in the second of dizygous twins (Tanner and Hewlett, 1935; Bradbury, 1977).

Despite the placenta being a preferential site for the malarial parasite, in only 11 of the 107 cases of congenital malaria reviewed by Covell, and in only one of the 9 cases reported in the United Kingdom (Meerstadt and Wright, unpublished data) was routine examination of the placenta for parasites performed. In pregnant mothers who have recently returned from malarious areas the routine screening of placental tissue blood and cord blood would lead to an earlier diagnosis of possible congenital malaria and permit closer observation of those infants at risk.

Interestingly, antimalarial treatment of infants at birth was not considered in any of the recently reported cases of congenital malaria in the United Kingdom or in the United States of America. In non-endemic areas those infants born to

mothers who have a parasitaemia, or who have a demonstrable placental infection, or cord blood parasitaemia or high specific IgG antibody levels should receive a curative course of antimalarial treatment. Specific IgM antibodies have not proved to be of value in the diagnosis of some cases of congenital malaria (Reinhardt, 1978; Hindi and Azimi, 1980) as transmission is often conatal rather than truly congenital.

Congenital malaria rarely presents before three weeks of age even when the mother has an active parasitaemia. The mean time to presentation in the nine United Kingdom cases was 31 days and in partially immune mothers the latent period can be much longer. The non-specific presentation may lead to the diagnosis being missed if there is no recent history of exposure, or history of malaria in pregnancy and if the parasites are not seen on routine blood films. Such a presentation with accidental diagnosis on routine blood films occurred in 6 of the 9 United Kingdom cases.

The definitive diagnosis of malaria is made on thick and thin film slide microscopy. Slides should be made fresh because the transportation of blood in EDTA, heparin and sodium oxalate causes morphological distortion of the parasites making species identification difficult or impossible (Ree and Sargeaunt, 1976).

TREATMENT

In 1957 resistance of *P. falciparum* to chloroquine was first reported in South America and South East Asia (Moore and Lanier, 1961). Similar resistant strains, as defined by the WHO criteria (WHO, 1973), have been reported in Sub-Sarahan Africa and particularly in East Africa (Campbell, 1979). Fortunately the other three strains of malarial parasite have remained sensitive to chloroquine.

Chloroquine is the drug of choice unless resistance or cerebral malaria is suspected. It is available in the salt or base form and should be given enterally if possible – chloroquine base 10 mg/kg followed by 5 mg/kg at 6 hours, 24 hours and 48 hours after the first dose. Parenteral preparations are available but their use should be avoided in view of their neurotoxic side effects. Convulsions and death have followed parenteral use (Geddes, 1970).

If chloroquine resistance is supected quinine sulphate should be used 5 - 10 mg/kg orally 8 hourly until blood fims are clear of asexual forms of the parasite. The use of parenteral quinine dihydrochloride is limited by its cardiotoxic and neurotoxic side effects, and should be reserved for cases of severe illness with heavy parasitaemia, cerebral malaria, where there is failure of clinical response, or where the enteral route is not appropriate. Quinine 5 - 10 mg/kg as an infusion over four hours should be given 12 hourly (Hall, 1976). If the parenteral preparation is used blood should be taken daily, immediately prior to the commencement of the infusion, for quinine levels (therapeutic range 18-30 micromols/l). The dosage should be adjusted accordingly bearing in mind that quinine is excreted by the liver. The quinine infusions should be continued until the blood films are clear of asexual forms. The sexual forms – the gametocytes – may take some further days to disappear. Once the course of quinine is completed a single dose of pyrimetha-

mine/sulphadoxine should be given orally – pyrimethamine 1 mg/kg and sulphadoxine 20 mg/kg. It is said that primaquine is not necessary since congenital malaria does not have an exoerythrocytic (liver) stage.

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