Prospective surveillance of neonatal meningitis

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Abstract

Neonatal meningitis is a serious problem with a high mortality and frequent neurological sequelae. The incidence of neonatal meningitis was calculated and the aetiology, clinical and laboratory features, and the treatment of cases recorded prospectively over a 7 year 8 month period was documented. It was further investigated whether secondary meningitis had occurred after lumbar puncture.

The estimated incidence of bacterial, viral, and fungal meningitis was 0.25, 0.11, and 0.02 per 1000 live births respectively. There were eight cases of early onset meningitis (seven definite, one probable) and group B streptococci accounted for six (75%) of these. Blood cultures were negative in only one of seven cases of definite early bacterial meningitis. Of the 15 late onset cases, Gram negative organisms accounted for six of the seven bacterial cases. The overall mortality was 26%. Of the 11 survivors of bacterial meningitis, three (27%) had significant neurological sequelae at follow up (between three months to three years later).

As in the first 48 hours after birth an initial blood culture is unlikely to be negative if bacterial meningitis is present, lumbar puncture can be deferred if the procedure might exacerbate respiratory distress. Although approximately 1880 infants had a lumbar puncture during the review period, only one case of meningitis was found where it was possible that lumbar puncture in a bacteraemic infant may have caused meningeal infection. The incidence of this potential complication must therefore be low.

(Arch Dis Child 1993; 69: 14-18)

Despite considerable progress in antimicrobial and supportive treatment, meningitis remains a serious problem in newborn infants, with a high mortality and frequent neurological sequelae. About 20-30% of neonatal septicaemia, whether early or late, is complicated by bacterial meningitis.^{1,2} Studies based on a geographically defined population in the USA have shown 0.2-0.5 cases of bacterial meningitis per 1000 live births.^{1,3} Reviews from Europe,⁴⁻⁶ and Australia⁷ present similar rates of infection, and a recent study by de Louvois and Harvey suggests that the incidence in England and Wales is about 0.4 per 1000 live births.⁴

Several studies report that preterm birth and low birth weight are the most common perinatal factors associated with developing meningitis in the newborn.^{1,2,4,8} There have

been occasional reports of infants who have developed meningitis after a lumbar puncture performed during bacteraemia.^{9,10}

The aims of this study were to estimate the incidence and document the aetiology, clinical and laboratory features, mortality, and developmental outcome of neonatal cases of meningitis, recorded prospectively over a 7 year 8 month period in the neonatal unit, John Radcliffe Maternity Hospital, Oxford. Because it is postulated that lumbar puncture in a bacteraemic infant may lead to meningitis, we investigated whether secondary meningitis had occurred after a traumatic tap.

Subjects, definitions, and methods

All babies admitted to the neonatal unit during the period May 1984 - December 1991 with definite or probable neonatal bacterial, viral, or fungal meningitis were included in the study. Cases of ventriculoperitoneal shunt infection were excluded, as was meningitis occurring in an infant >28 days after birth.

Early onset infection was defined as beginning before 48 hours after birth. *Late onset* infection began after 48 hours, but before 28 days after birth. Analysis of cerebrospinal fluid (CSF) in the laboratory was carried out by Gram stain of a centrifuged deposit, cell count, protein, and glucose estimation, as well as standard bacteriological and viral methods of inoculation, culture, and identification. Primary bacterial cultures were performed by the inoculation on to horseblood and chocolate plates of the centrifuged deposit. Enrichment cultures were carried out by the inoculation of a deposit on to a tryptone soy broth.

Definite bacterial meningitis was diagnosed if there was pure growth of a pathogen from primary CSF culture (or postmortem culture if a lumbar puncture had not been possible) and a supportive clinical picture, for example thermal and respiratory instability, feed intolerance, and seizures.

Probable bacterial meningitis was diagnosed if no organism was obtained from primary CSF culture, but there was either a positive Gram stain or a pathogen grown on enrichment culture and the history or clinical condition was suggestive of meningitis.

A contaminant was defined by growth of an organism only in enrichment broth without pleocytosis or positive Gram stain, together with a clinical picture not suggestive of meningitis.

Definite viral meningitis was diagnosed if meningitis was suggested clinically and a virus was isolated from CSF. If CSF was sterile, virus isolation from other sources (blood, urine, breast milk, stools, surface swabs) or a CSF lymphocytosis, together with suggestive

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Accepted 18 March 1993

clinical symptoms was defined as a case of *probable* viral meningitis. Neurological and developmental outcome as determined at clinical follow up by a paediatrician was ascertained from case records.

Results

Over the 7 year 8 month period, 52 970 babies were born at the John Radcliffe Maternity Hospital, Oxford and of these, 20 developed meningitis. Thus the overall incidence for inborn babies was 0.38 per 1000 live births. Three further cases occurred in babies transferred into the unit. Bacterial infection occurred in 15 infants (11 definite, four probable; two were transfers), viral in six (two definite, four probable), and fungal in two (both definite; one was a transfer). The incidence of each infection per 1000 live births was 0.25, 0.11, and 0.2 respectively (transfers excluded). The organisms causing meningitis and associated mortality are shown in table 1. Among cases of bacterial meningitis, group B streptococci were the most common cause (seven cases). As a group, Gram negative bacteria were also a common cause (six cases), though no one organism predominated. Viral meningitis accounted for six (26%) of the total number of cases, and fungal infections for two (9%). The male:female ratio for bacterial meningitis was 2.8:1 and for viral meningitis 1:2. The mean birth weight for all cases of meningitis was 2091 g (range 554–3227) and the mean gestational age was 33 weeks (range 24–40).

Table 1 Neonatal meningitis: causes, onset, and outcome

Causative organism	No of cases		
	Early	Late	Total
Bacterial (total)	8 (2)*	7 (2)	15 (4)
Group B streptococcus	6 (2)	1	7
Gram negative		6 (2)	6
<i>Pseudomonas aeruginosa</i>		1 (1)	
<i>Klebsiella oxytoca</i>		2	
<i>Serratia liquefaciens</i>		1 (1)	
<i>Achromobacter xylosoxidans</i>		1	
Undefined rod		1	
<i>Streptococcus mitis</i>	1		1
<i>Listeria monocytogenes</i>	1		1
Viral (total)		6	6
Echo		2	
Coxsackie		2	
Undefined		2	
Fungal			
<i>Candida albicans</i>		2 (2)	2 (2)
Total	8 (2)	15 (4)	23 (6)

*Fatal cases in parentheses.

Table 2 Cases of neonatal meningitis classified by cause, birth weight, gestational age, and time of onset

	Early onset			Late onset		
	Bacterial	Fungal	Viral	Bacterial	Fungal	Viral
Birth weight (g)						
<1500	1 (1)*	–	–	4 (1)	2 (2)	1
1500–2499	2 (1)	–	–	2 (1)	–	2
≥2500	5	–	–	1	–	3
Gestational age (weeks)						
<37	3 (2)	–	–	6 (2)	2 (2)	4
≥37	5	–	–	1		2

*Fatal cases in parentheses.

PREDISPOSING FACTORS, ONSET, AND CLINICAL MANIFESTATIONS

The most frequent predisposing factors for meningitis were: (i) prematurity (n=15); (ii) presumed maternal infection (chorioamnionitis or maternal pyrexia) (n=5); and (iii) prolonged rupture of membranes >24 hours (PROM) (n=4).

There were eight cases of early onset meningitis (seven definite, one probable) and group B streptococci were responsible for six of these (table 1). There were 15 late onset cases and Gram negative organisms accounted for six of the seven bacterial cases (86%).

Taking into account all cases of late onset meningitis, 12 of 15 (80%) were preterm (gestational age <37 weeks) and seven (47%) had a very low birth weight (<1500 g).

Of the four infants born after PROM, three had early onset of clinical symptoms and the fourth, though well, had group B streptococci cultured from CSF enrichment broth after lumbar puncture on day 1. Of the five babies born to mothers with presumed infection, three had early onset bacterial meningitis and two developed viral meningitis within five days of birth. The distribution of meningitis, relating to onset of symptoms, birth weight, and gestational age is shown in table 2.

The most frequent presenting signs were pyrexia (n=17), bradycardia (n=10), apnoea (n=8), irritability (n=8), and convulsions (n=7). Less common signs were bulging fontanelle (n=5) and high pitched cry (n=3). Seizures occurred in seven infants with bacterial infections: four with group B streptococci and three with Gram negative bacillary meningitis. None of the babies had clinical neck stiffness. None of the viral or fungal cases presented with convulsions.

LABORATORY FINDINGS

Of the 15 babies with bacterial meningitis, 10 had simultaneously positive blood and CSF cultures. One baby with early onset group B streptococcal infection lived only 40 minutes, and a lumbar puncture was not done before death, but the baby had evidence on postmortem examination of meningitis. One baby with late onset probable Gram negative bacillary meningitis had negative CSF and blood cultures, but the clinical picture was suggestive of meningitis and CSF obtained while on antibiotic treatment was positive by Gram staining. Three neonates had negative blood culture, with positive CSF result; two were probable infections (late *Klebsiella oxytoca* and early group B streptococcus and only one was definite (early *Streptococcus mitis*). The mother of the definite case was not treated with antibiotics before delivery and neither was the mother of the baby with probable early group B streptococcal infection. The baby with probable group B streptococcus was not clinically ill, did not have a high white blood cell count, but was born after PROM to a mother with a febrile illness and CSF enrichment culture was positive.

One term baby with late *K oxytoca* infection had positive blood culture, but concurrent CSF culture was negative, although the tap was traumatic. As the child appeared unwell again two days later, a repeat lumbar puncture was performed and this grew the same organism, *K oxytoca* (with the same antibiotic sensitivities) as originally was isolated from the blood.

None of the six infants with viral meningitis had positive blood culture for bacteria; virus was isolated from the CSF in two, from the stools in three others, and not at all in the sixth case (where CSF lymphocytosis suggested the diagnosis). Both cases of fungal meningitis grew *Candida albicans* in the CSF, but only one had a simultaneously positive blood culture.

CSF white cell count

The white cell count in the CSF was $>100 \times 10^6/l$ in 16 infants. In four cases the white cell count was not available: three because of unsuitable samples (heavily blood stained or clotted) and one because meningitis was not proved until postmortem examination. In three cases (two bacterial and one viral) the CSF white cell count was minimally raised ($25-50 \times 10^6/l$). One of the bacterial cases with minimally raised CSF white cell count was considered a definite early onset group B streptococcal infection while the other was a partially treated probable Gram negative bacillary meningitis with negative CSF culture, but positive Gram stain. The viral case with minimally raised CSF white cell count was considered probable because, although CSF was culture negative, clinical signs were suggestive of infection, and Coxsackie B6 virus was isolated from stools. The range of white cell counts in the CSF in the bacterial cases of meningitis was $28-4240 \times 10^6/l$, and in the viral cases was $44-464 \times 10^6/l$.

TREATMENT OF BACTERIAL MENINGITIS

All patients received combination antibiotic treatment, at least initially. Of the 11 children with bacterial meningitis who completed treatment eight were treated for 21 days, and three (one probable Gram negative and two definite group B streptococcal infections) were treated for 10-14 days. None of these relapsed. The initial choice of antibiotic treatment was based on the unit's standard policy¹¹: penicillin and gentamicin (netilmicin from November 1986) for early infection, and flucloxacillin and gentamicin/netilmicin for late infection. Treatment was adjusted according to Gram stain, culture, and sensitivity results. Group B streptococcal meningitis cases completed treatment with either penicillin alone or penicillin and gentamicin (or netilmicin). The child with *Listeria monocytogenes* meningitis was treated with ampicillin and netilmicin. All six cases of Gram negative meningitis were late in onset and treated initially with flucloxacillin and gentamicin (or netilmicin) if the Gram stain was negative or with a third generation cephalosporin and gentamicin (or netilmicin)

when CSF Gram stain was positive. No babies were given antibiotics by the intrathecal or intraventricular route and none was treated with chloramphenicol. Steroids were not used.

The viral cases of meningitis were treated with antibiotics for 5-7 days until the enriched bacterial culture was negative at which time viral culture results were often available. The two cases of candida meningitis were treated with amphotericin B for three weeks and one also received 5 fluorocytosine simultaneously.

OUTCOME

The relationship between mortality, the time of onset of infection, and the causative organism is shown in table 1. Six of the 23 babies died (26%): four with late and two with early onset infection; all were preterm (gestational age <37 weeks) and had a birth weight <2000 g. All four fatal cases after late onset infection occurred in babies <32 weeks' gestation (table 2). The male: female ratio of fatal cases was 1:2. Four of the fatal cases were bacterial (two group B streptococcal and two Gram negative) and two were fungal infections. The diagnosis was confirmed by positive CSF culture during life in all infants except one, who died soon after birth and had evidence of infection on postmortem examination.

All surviving infants except one (who moved away) were followed up for periods of between three months and three years. None of the six viral cases died or had long term sequelae. Eight of the 11 survivors of bacterial meningitis had an apparently good outcome without serious handicap, although one had an intermittent squint, one had an uncomplicated febrile convulsion at eight months after birth, and another had transient ventricular dilatation. Three survivors (27%) developed hydrocephalus requiring ventriculoperitoneal shunt insertion. One of the three also had cerebral atrophy, hemiparesis, and impairment of both vision and hearing.

Discussion

Although neonatal meningitis has a high mortality and a significant risk of long term neurological sequelae, it is thought to be under reported in England and Wales.⁴ The incidence of neonatal bacterial meningitis in this study (0.25/1000 live births) is similar to that reported in two large series by de Louvois and Harvey (0.32/1000 live births) for the period 1985-74 and by Goldacre (0.26/1000 live births) for the period 1969-73.¹² Infants born at 30 weeks' gestation or less are at particular risk of intraventricular haemorrhage in the first two days after birth,¹³ and these infants often have lumbar puncture deferred, even though the suspicion of meningitis is present within those first two days. It is highly likely that a number of infants with meningitis had lumbar puncture deferred and a diagnosis was never made as antibiotic treatment was given for an associated bacteraemia. Neonates who developed meningitis after discharge from hospital were not admitted to the neonatal unit. Thus,

the true incidence of neonatal meningitis is likely to be higher than we have calculated.

Early diagnosis of neonatal meningitis deserves a high priority. Clinical examination cannot distinguish septicaemic babies with coexisting meningitis from those without meningitis. As reported by some authors, in 15% of neonates with meningitis, blood culture is negative.¹⁴ Our review documented three cases (13%) of bacterial meningitis (one probable early group B streptococcal, one definite early *S. mitis*, and one probable late *K. oxytoca*) with positive CSF culture and negative blood cultures. The results of lumbar puncture directed the choice of antibiotic treatment and its duration. All these babies had a good outcome with no neurodevelopmental impairment. Blood cultures were negative in only one of seven cases of definite early bacterial meningitis during the seven year period. In the first 48 hours after birth, lumbar puncture may therefore be deferred if the clinical condition is poor. A bacteriological diagnosis can rest on blood cultures which, if positive, should be an indication for lumbar puncture when judged prudent and if this is not possible the child should be treated as if meningitis were present with 2–3 weeks of intravenous antibiotics.

This study showed that meningitis occurred most frequently among preterm infants (61%), which is consistent with previous reports.^{4 10} Group B streptococci were the most common cause of early onset bacterial meningitis (75%). The high mortality associated with early onset meningitis caused by group B streptococci is consistent with previous reports^{4 15} and underlines the importance of prevention and the need to provide good activity against group B streptococci in antibiotic regimens given soon after birth. Antibiotic treatment for late onset infections should provide good activity against Gram negative organisms as these were the most common cause (table 1).

The combined mortality rate associated with bacterial and fungal infection was similar to that reported in other studies.^{3 5} Mortality was higher among the late onset group and in this group occurred exclusively in preterm babies with a birth weight <2000 g and gestational age <32 weeks, whose CSF cultures were positive.

Sixteen of the 17 surviving infants were followed up as outpatients. The observed rate for moderate to severe neurological sequelae represents a minimum estimate of morbidity. It is similar to other reports.^{2 16}

Candida meningitis has been reported to be an increasing problem, particularly in preterm infants with very low birth weight who require parenteral nutrition and long courses of antibiotics.¹⁷ Our two cases both fit this description. Both of them died. The symptoms associated with fungal meningitis are very similar to those seen in bacterial meningitis and the clinician needs to be aware of this possibility in very low birthweight infants. In our unit we have also recently seen two cases of disseminated *Candida* infection (not included in this review) in very preterm infants, both of

whom had cerebral abscesses and died. Vigilance for the possibility of central nervous system infection by *Candida* is clearly important.

The diagnosis of meningitis cannot be excluded by normal CSF chemistry or a normal CSF white cell count.^{11 18 19} Because of this, antibiotic treatment is given until culture results are available. Our review found two cases of bacterial meningitis where CSF white cell count was minimally raised ($25\text{--}50 \times 10^6/l$), but the CSF culture result was positive in one, whereas in the other, only Gram stain was positive, the child having been previously treated with antibiotics. A low CSF white cell count in the presence of infection can be explained by previous treatment, or on the grounds that an inflammatory response has not yet been mounted. It is also possible that a traumatic lumbar puncture performed in a child who does not have meningitis, but does have bacteraemia, could result in an apparently positive CSF culture. Furthermore, clinical meningitis could develop as a result of the blood being introduced into the cerebrospinal fluid. However, meningitis may evolve in a bacteraemic baby in the usual way irrespective of a lumbar puncture.

The possibility that lumbar puncture performed during bacteraemia may cause meningitis has been suggested in previous studies.^{9 10 19} It may be that trauma to the meninges by lumbar puncture does facilitate seeding of the CSF. To determine whether this is a clinically important association is extremely difficult and we can only speculate. In this study, covering almost eight years, only one possible case was found. We have estimated that 1880 infants had a lumbar puncture during the review period. This suggests that the incidence of meningitis secondary to lumbar puncture is very low.

We are very grateful to Dr David Isaacs for his advice and contribution to neonatal infection surveillance.

We also thank the staff of the neonatal unit and of the Oxford Public Health Laboratory Service. Finally, we thank Mrs C Barr for typing the script.

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