Infantile meningitis in England and Wales: a two year study

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Abstract

A two year prospective study identified 1922 cases of meningitis in children under 1 year of age. A further 201 cases were identified from other sources. The annual incidence of meningitis during the first year of life was 1.6/1000; during the first 28 days of life it was 0.32/1000, and among postneonatal infants it was 1.22/1000. The male:female ratio was 1.4:1. The overall case fatality rate was 19.8% for neonates and 5.4% for postneonatal infants. Two thirds of deaths identified in the study, 50% of all deaths, were not attributed to meningitis by the Office of Population Censuses and Surveys. Group B β haemolytic streptococci (28%), *Escherichia coli* (18%), and *Listeria monocytogenes* (5%) were most frequently isolated from neonates and *Neisseria meningitidis* (31%), *Haemophilus influenzae* (30%), and *Streptococcus pneumoniae* (10%) from postneonatal infants. At 2-6 months of age *N meningitidis* meningitis was most common, and at 7-12 months *H influenzae* predominated. Meningitis caused by group B β haemolytic streptococci occurred up to 6 months of age and had a consistent mortality of 25%. Neonatal meningitis due to Gram negative enteric rods had a mortality of 32%. Low birth weight was a significant predisposing factor for both neonates and postneonatal infants. In both groups mortality was significantly higher among children admitted in coma. There was no seasonal variation in incidence in either group. Neonates were treated with either chloramphenicol (50%) or gentamicin (48%) usually in combination with a penicillin; 40% received a third generation cephalosporin. Of the 1472 postneonatal infants treated 84% received chloramphenicol with a penicillin and 10% received a third generation cephalosporin. Relapse occurred in 49 patients and three died. Eighteen babies coned as a result of raised intracranial pressure, including four neonates, and four died. Mortality among the 133 (7%) children who received steroids was significantly higher than in the rest of the study group.

Meningitis in infancy is a life threatening infection with a high mortality. Neurological sequelae are common, especially in the newborn where long term effects are found in more than a quarter of survivors.^{1 2} Despite its serious nature there is little information on the incidence of meningitis in England and Wales. Although a number of centres, including the Communicable Diseases Surveillance Centre of

the Public Health Laboratory Service and the Meningococcal Reference Laboratory, collect data provided to them on a voluntary basis there is known to be considerable under reporting. There is a high level of under reporting also in local studies, even for meningococcal meningitis.³⁻⁶ The only comprehensive information on the recent incidence of meningitis in Great Britain comes from a few independent studies with small numbers of patients. A study of cases from the North West Thames health region for the period 1969-73 identified 76 cases in newborn babies and 231 cases in postneonatal infants (28-365 days of age); the case fatality rates were 43% and 13% respectively.⁷ The incidence of meningitis in the newborn was 0.26/1000 live births. Meningitis was diagnosed only at necropsy in 28% of fatal cases; many of them were not indexed by Hospital Activity Analysis (HAA).

The present study was undertaken to determine prospectively the incidence of meningitis among children under 1 year of age in England and Wales.

Subjects and methods

STUDY ORGANISATION

With the collaboration of 566 consultant paediatricians we undertook to identify all cases of acute meningitis in children under 1 year of age in England and Wales from September 1985 to August 1987. At the beginning of each month each paediatrician received a prepaid card which inquired whether they had managed any cases of acute infantile meningitis during the previous month. After each notification, clinical and laboratory information was collected on standard forms sent to the paediatrician and consultant microbiologist involved in the management of each case. Written permission was obtained from the paediatricians so that information on cases notified in confidence to the Communicable Diseases Surveillance Centre, Colindale (CDSC) and the Meningococcal Reference Laboratory, Manchester, could also be used. Death certificates on all babies recorded as having died of meningitis were obtained from the Office of Population Censuses and Surveys (OPCS).

ADMISSION CRITERIA

The initial criterion for inclusion in the study was an 'intention to treat' by the paediatrician of babies with clinical signs and symptoms suggestive of meningitis. Babies who had viable bacteria, viruses, or detectable bacterial antigen in

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Accepted 10 December 1990

the cerebrospinal fluid or whose white cell counts in the cerebrospinal fluid were sufficiently abnormal ($>20 \times 10^6/l$) to warrant a diagnosis of meningitis were finally accepted into the study. Babies whose clinical condition was highly suggestive of meningitis but who were deemed too ill to warrant a lumbar puncture were also included. Babies with spina bifida and ventricular shunt infections were excluded.

Bacterial isolates and residual samples of cerebrospinal fluid were sent to our centre when available. No attempt was made to influence the management or treatment of babies admitted to the study nor to alter the protocol for local laboratory investigations carried out on samples.

Results

The monthly inquiry cards identified 1922 cases of meningitis in England and Wales during the two year period. Information on 201 additional cases (23 neonates; 133 postneonatal infants between 1 month and 1 year of age, and 45 infants of unspecified age under 1 year) was obtained from the CDSC (n=138), the Meningococcal Reference Laboratory (n=27) and the OPCS (n=36). These 201 cases are included in the calculation of incidence and mortality but are excluded from other analysis. Information from all sources identified a total of 2123 cases of meningitis during the first year of life. The mean birth rate for England and Wales during the study period was 658 700 per annum; giving an annual incidence of meningitis during the first year of life of 1.61/1000. There were 423 cases during the first 28 days of life (an inci-

dence of 0.32/1000) and 1605 cases in the period 29–365 days (an incidence of 1.22/1000 population). There were another 95 cases (50 from the survey and 45 from other sources) among babies less than 1 year of age whose exact age was not known. The male:female ratio was 1.4:1 for both neonates and postneonatal infants. Culture results for the cases identified from all sources are shown in table 1.

Of the 1922 cases of meningitis identified in our study, 400 were in babies less than 29 days of age and 1472 were aged 29–365 days. After the initial notification no further information was obtained on the remaining 50 babies and these are omitted from further analysis. The overall case fatality rate was 79/400 (19.8%) for neonates and 5.4% (79/1472) for postneonatal infants. A total of 104 of 158 deaths (66%) identified by us were not coded as attributable to meningitis by OPCS. They account for 51% (104/201) of all deaths from meningitis in children under 1 year of age. In addition, 12% of the death certificates coded by OPCS as cases of meningitis contained no mention of the condition. Among the deaths notified to OPCS were 23 which were not notified to the study. Some of these are known to be infants who did not come to the attention of the paediatricians. Among babies whose cerebrospinal fluid cultures were positive, the overall mortality rate was 10% (29% for neonates and 6% for postneonatal infants) in bacterial meningitis and nil in viral meningitis. There was a significantly higher mortality among babies with viable bacteria in the cerebrospinal fluid compared with those with only a pleocytosis; for neonates ($p<0.0001$, odds ratio 10.44, confidence intervals 3.1 to 34.8); and for postneonatal infants ($p<0.001$, odds ratio 3.59, confidence intervals 1.4 to 9.1). White cell counts in the cerebrospinal fluid were $>100 \times 10^6/l$ in 79% of neonates and 85% of postneonatal infants. Only 8.5% of neonates and 6% of infants with culture positive meningitis had cerebrospinal fluid cell counts $<10 \times 10^6/l$.

Clinical details on the 1872 patients at the time of diagnosis are shown in table 2. Prematurity and low birth weight were predisposing factors in both the neonatal and the postneonatal infants groups. A birth weight of <2000 g was significantly more common in both patient groups ($p<0.001$) than the 2.4% of the population in England and Wales with a birth weight of <2000 g.⁸ Meningitis was 10 times more common among neonates weighing <2000 g than those of >2000 g birth weight.

Table 1 Meningitis in the first year of life in England and Wales 1985–7: causative organisms. Results are number (%)

	Neonates (n=423)	Postneonatal infants (n=1605)
Group B β haemolytic streptococci	118 (28)	50 (3)
<i>Escherichia coli</i>	78 (18)	29 (2)
<i>Listeria monocytogenes</i>	23 (5)	1 (<1)
<i>Haemophilus influenzae</i>	9 (2)	477 (30)
<i>Neisseria meningitidis</i>	11 (3)	490 (31)
<i>Streptococcus pneumoniae</i>	19 (5)	158 (10)
Other Gram positive bacteria	15 (4)	26 (2)
Other Gram negative bacteria	28 (7)	31 (2)
Viruses	16 (4)	37 (2)
<i>Mycoplasma hominis</i>	3 (<1)	1 (<1)
<i>Candida albicans</i>	4 (1)	5 (<1)
Other microorganisms	5 (1)	9 (<1)
Cerebrospinal fluid sterile or not collected	92 (22)	270 (17)
Unknown	2 (<1)	21 (1)

Table 2 Clinical details at the time of diagnosis on 1872 babies with meningitis. Results are number (%)

	Total (n=1872)	Neonates (n=400)	Postneonatal infants (n=1472)
Less than 30 weeks' gestation	75	37 (9)	38 (3)
Less than 2000 g at birth	163	78 (20)	85 (6)
On admission:			
In coma	205	42 (11)	163 (11)
Convulsions	325	82 (21)	243 (17)
Rash	248	18 (5)	230 (16)
Antibiotic treatment in previous 48 hours	420	82 (21)	338 (23)
Congenital anomaly	107	29 (7)	78 (5)
Hydrocephalus	46	12 (3)	34 (2)
Previous surgery	68	13 (3)	55 (4)
History of otitis media	120	0	120 (8)
Antecedent history	275	39 (10)	236 (16)

Among postneonatal infants the ratio was 2.5:1. Twelve per cent of neonates and postneonatal infants were admitted in coma; in both groups, this was associated with a significantly increased mortality ($p<0.0001$). A rash was present at diagnosis in 16% of infants, but only 5% of neonates. All of the babies with a history of otitis media were in the infant group. Recent upper respiratory tract infection or other antecedent history of infection was also more common among infants (16%) than neonates (10%). Altogether 94% of infants and 45% of neonates with meningitis were admitted from home and 23% had received antibiotics from the general practitioner before admission. There was no seasonal variation in incidence of meningitis in either group of patients.

Seventy one babies did not have a sample of cerebrospinal fluid taken before treatment, because either they were considered to be too sick or the procedure failed; 23/71 (32%) of these babies died compared with 7% of babies who had cerebrospinal fluid collected. Mid-treatment samples of cerebrospinal fluid were collected from 41% of patients and samples after treatment from 20%.

Most patients received more than one antibiotic, only 172 (1%) received monotherapy. The number of babies who received each antibiotic and the percentage of neonates and infants treated with each antimicrobial agent are shown in table 3. In half the neonates the regimen was based on chloramphenicol and in half on gentamicin. In addition most patients received penicillin, ampicillin, or a third generation cephalosporin.

Among infants chloramphenicol was the most widely used antibiotic (84%) usually in combination with penicillin or ampicillin. Third generation cephalosporins were used for the treatment of 46% neonates but only 14% of postneonatal infants. No babies received cephalosporin only. Sulphonamides were included in the treatment regimens of 11% neonates and 17% of postneonatal infants.

Fifty eight per cent of patients were treated for seven to 14 days and 12% for 21 days. Altogether 29% of neonates compared with 14% of postneonatal infants were treated for more than 14 days. Antibiotic treatment was changed after sensitivity testing in 15% of neonates and 6% of postneonatal infants. Seven hundred and thirteen patients received barbiturates (50% of neonates and 40% of postneonatal infants) and

133 received steroids (7% of neonates and 8% of postneonatal infants); included in these figures are 96 patients who received both. Ten per cent of neonates and 26% of postneonatal infants who died had received steroids. Convulsions at the time of diagnosis were reported in 325 babies, 17% of the study population. Postmortem examinations were carried out on 70/159 babies who died (44%).

Ventriculitis, hydrocephalus, or convulsions were reported as complications in 346 (21%) of patients and were more common in the newborn (33%) than in postneonatal infants (18%). Forty nine patients relapsed after treatment: 15 (5%) neonates and 34 (3%) postneonatal infants; three of these died. Among patients who relapsed 21% were in coma on admission compared with approximately 11% for the total group; 25% had already received treatment for more than 21 days compared with 6% for the total population. Only 9% of patients who relapsed received antibiotics before admission compared with more than 20% of the total population. The white cell count in the cerebrospinal fluid among patients who relapsed was not different from that of the total population. Thirty one (86%) had cell counts $>100 \times 10^6/l$ cerebrospinal fluid at the time of the first diagnostic tap compared with 81% of the total population.

Paediatricians reported that 18 babies coned after lumbar puncture (four neonates and 14 postneonatal infants) as a result of raised intracranial pressure; four of them died. All the babies who coned weighed more than 2000 g at birth but three were less than 36 weeks' gestation. Twelve (66%) were feverish ($>38^\circ C$) at the time of diagnosis and only one had received antibiotics during the previous 48 hours, four were admitted in coma, four had convulsions, and one had a rash. None of the patients who coned had a congenital anomaly, one had developed hydrocephalus before admission, and one had a history of otitis. Results from the cerebrospinal fluid were available from 15 of the patients who coned; in 14 (93%) the white cell count was $>100 \times 10^6/l$. The course of the illness for 12/16 (75%) patients who coned was complicated by convulsions, ventriculitis, or hydrocephalus compared with 21% of the total population. Information on the other two patients was not available. Two patients relapsed after treatment was completed.

The organisms isolated from the cerebrospinal fluid are shown in table 1. Among neonates, group B β haemolytic streptococci were most frequently isolated followed by *E coli* and *L monocytogenes*. A wide range of other bacteria were implicated in neonatal meningitis whereas among postneonatal infants *N meningitidis*, *H influenzae* and *S pneumoniae* accounted for 70% of all cases and 89% of bacteriologically proved meningitis. The case fatality rate was highest in neonates with meningitis due to enteric Gram negative rods: 32% compared with 22% for group B β haemolytic streptococcal meningitis, 5% among cases due to *L monocytogenes*, and 2% among culture negative cases.

E coli and group B β haemolytic streptococci were also significant causes of meningitis

Table 3 Antibiotic treatment of 1872 babies with meningitis. Results are number (%)

	Total (n=1683* 1872)	Neonates (n=360* 400)	Postneonatal infants (n=1323* 1472)
Chloramphenicol	1293	180 (50)	1113 (84)
Gentamicin	284	174 (48)	110 (8)
Other aminoglycosides	45	30 (8)	15 (1)
Penicillin	1220	225 (62)	995 (75)
Ampicillin	377	79 (22)	298 (23)
Other penicillins	46	27 (7)	19 (1)
Cefotaxime	202	94 (26)	108 (8)
Ceftazidime	84	54 (15)	30 (2)
Other cephalosporins	71	20 (5)	51 (4)
Sulphonamides	259	40 (11)	219 (17)
Other antibiotics	18	9 (2)	9 (1)

*Patients with treatment data.

Table 4 Meningitis in the first year of life in England and Wales 1985–7: death by organism. Results are number (%)

	Neonates (n=400)	Postneonatal infants (n=1472)
Group B β haemolytic streptococci	27/112 (24)	11/44 (25)
<i>Escherichia coli</i>	18/72 (25)	5/27 (19)
<i>Listeria monocytogenes</i>	2/19 (11)	0/1
<i>Haemophilus influenzae</i>	2/9 (22)	17/445 (4)
<i>Neisseria meningitidis</i>	0/10	19/433 (4)
<i>Streptococcus pneumoniae</i>	3/18 (17)	12/150 (8)
Other Gram negative organisms	13/26 (50)	5/27 (19)
Other Gram positive organisms	5/14 (36)	3/23 (13)
Viruses	0/16	0/37
<i>Mycoplasma hominis</i>	2/3 (66)	0/1
<i>Candida albicans</i>	3/4 (75)	1/5 (20)
Other microorganisms	1/5 (20)	1/9 (11)
Sterile cerebrospinal fluid	3/92 (3)	5/270 (2)
Total No deaths	79	79

outside the neonatal period and together accounted for 8% cases during the second to sixth months of life. Throughout the first year of life meningitis due to *E coli* and group B β haemolytic streptococci was associated with a high mortality rate. Cases and deaths by organism for patients in the two groups are shown in table 4. Meningitis was most common during weeks one and three of life. *N meningitidis* (29%) was the commonest cause of meningitis in children 2–6 months of age, and among children aged 7–12 months *H influenzae* (46%) was most frequently isolated. The mortality rate among postneonatal infants infected with *S pneumoniae* was twice as high (6%) as that after infection with meningococci or haemophilus.

Discussion

This study confirms recent reports that meningitis in England and Wales is still significantly under reported.^{3–6} Detailed observations on reporting will be the subject of a separate communication. Information on a large number of cases notified to us was not sent to CDSC or the Meningococcal Reference Laboratory. Consultant paediatricians notified us of 158 babies who had died of meningitis; 104 (66%) of these were not coded by OPCS as cases of meningitis. In addition there were 43 children who died of meningitis, 22% of all deaths, who were not notified to the study. Subsequent inquiry revealed that many of these cases had not come to the attention of the paediatricians. This figure (22%) compares with the 29% reported by Goldacre for infants in whom meningitis was diagnosed only at necropsy.⁷ Accurate calculation of the mortality associated with meningitis during the newborn period is now impossible as OPCS no longer report the causes of death occurring during the first 28 days of life. It is disturbing that 12% of death certificates for babies coded by OPCS as having died from meningitis contained no mention of this condition.

The incidence of neonatal meningitis in our study (0.32/1000 live births) is higher than that reported by Goldacre (0.26/1000 live births) for the period 1969–73, using essentially the same diagnostic criteria.⁷ This would support the suggestion that the incidence of meningitis among the newborn is increasing; however,

comparison of the figures for the North West Thames hospital region for 1968–73 and 1985–7 shows no increase. There were 16 cases of neonatal meningitis per year for the period 1968–73 compared with 10 per year during 1985–7. Among postneonatal infants there were 46 and 40 cases per year respectively. Although there may have been no increase in the incidence of meningitis, the case fatality rate for neonatal meningitis has fallen from 43% reported by Goldacre to 20% in the present study. Among postneonatal infants the mortality rate has fallen from 13% for the period 1969–73 to 5% for the period 1985–7.

Meningitis occurred significantly more frequently ($p < 0.001$) among neonates who were born prematurely or were of low birth weight confirming previous reports.⁹ There was a significant association also ($p < 0.001$) between low birth weight (< 2000 g) and meningitis among postneonatal infants compared with the national incidence of birth weight below 2000 g.⁸ Meningitis due to Gram negative organisms has a higher mortality than that due to Gram positive bacteria, as has been reported previously.^{10, 11} Mortality is significantly lower for postneonatal infants in general but it remains high throughout the first year of life for babies infected with *E coli* and group B β haemolytic streptococci. Irrespective of the clinical presentation or the number of white cells present in the cerebrospinal fluid, mortality was significantly lower for both neonates and postneonatal infants whose cerebrospinal fluid culture results were negative. Some of these may have been cases of undiagnosed viral meningitis, and in others the prompt use of antibiotics by the general practitioner may have effectively sterilised the cerebrospinal fluid before a lumbar puncture was performed.

In the majority of laboratories in England and Wales viral studies are not part of the routine investigation of suspected infantile meningitis. Chonmaitree *et al* studied 111 patients who had viral investigations because of suspected meningitis; 63 of these patients were under 1 year of age.¹² Enteroviruses were isolated from 46 (41%) of the population and from 60% of those under 1 year of age. The isolation of a virus shortened hospital stay and reduced the unnecessary use of antibiotics. Clearly, viral culture of cerebrospinal fluid and other appropriate specimens, together with serology, should be part of the routine investigation of meningitis in the very young.

Only 133 (7%) of the study population received steroids during the acute phase of their illness. Mortality among those receiving steroids was significantly higher ($p < 0.001$) than for the remainder of the population. This is not in agreement with other studies and probably reflects the use of steroids in the most severely ill patients. In controlled studies on the use of dexamethasone in the treatment of meningitis, Lebel *et al* reported that administration before the first dose of antibiotics does not effect the mortality rate but reduces the duration of fever and significantly lowers the incidence of sensorineural hearing loss associated with acute bacterial meningitis.¹³ The beneficial effects of

dexamethasone have been reported by other workers also.^{14 15} No information is available on the duration of fever in the group treated with steroids in our study. We are currently following up the study population, and matched controls, until the fifth birthday in order to determine the incidence of deafness and other long term sequelae from infantile meningitis.

We thank all the paediatricians and microbiologists concerned in this study for allowing us to study their patients and for so willingly providing the information requested. Without their cooperation this study would not have been possible. The study was supported financially by donations received by the Karim Centre for Meningitis Research.

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Autism, gene pools, and the Mormons

Autism affects between two and five of every 10 000 and is three or four times more common in males than females.¹ The cause is unknown but genetic factors seem more important than acquired disease. The concordance rates are 64% in dizygotic and 9% in monozygotic twins. An epidemiological survey of the state of Utah has provided useful information. A total of 241 people with autism were ascertained and the medical records of 233 of them and of 62 of their non-autistic siblings were examined (Mason-Brothers *et al*, *Pediatrics* 1990;86:514-9). There were no significant differences between autistic and non-autistic subjects as regards prenatal, perinatal, or postnatal factors.

Previously published results from the same survey gave usable information for genetic counselling.² The recurrence risk overall was 8.6% but it varied according to the sex of the first autistic child; if the first child was male the recurrence risk was 7%, if female 14.5%. The authors are careful to point out that the strength of the Mormon church in Utah does not appear to have had any significant effect on the gene pool.

ARCHIVIST

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