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ORIGINAL PAPER

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Neonatal meningitis in England and Wales: sequelae at 5 years of age

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Abstract This study determined the prevalence of serious sequelae among a national cohort of 5-year old children, born in England and Wales in 1996–7, who had had neonatal meningitis. The results were compared with those from two matched control groups. In addition the results from this study were compared with those from a previous 5-year follow-up of children who had had neonatal meningitis in 1985–7. Follow-up questionnaires requesting information about the children's health and development were sent to the general practitioners (GPs) and parents of the index children and controls. Information was collected on 166 of 232 (72%) children who had had meningitis as neonates, 109 general practice controls and 191 hospital controls. At 5 years, 39/166 (23%) index children had a serious disability compared to 2% of GP controls and 7% of hospital controls. There was a 16-fold increase in risk of serious disability compared to GP-matched controls and a 4-fold increase in risk compared to hospital controls. The isolation of bacteria from the CSF was the best single predictor of serious long-term disability. Although there was a 70% fall in acute phase mortality between 1985 (22%) and 1996 (6.6%), the overall incidence of serious disability remained alarmingly high, 25.5% in 1985 compared to 23.5% in 1996. In the present study, however, fewer children had cerebral palsy or seizure disorders. *Conclusion:* Despite the dramatic improvement in acute phase survival following neonatal meningitis, the prevalence of serious sequelae remains alarmingly high.

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Abbreviations FET : Fisher's exact test · GBS : group B *Streptococcus* · GP : general practitioner

Introduction

In our national prospective study of neonatal meningitis in England and Wales carried out in 1996–7 [7], there was an acute phase mortality of 6.6% compared to a mortality of 22% in a similar study carried out in 1985–7 [9]. The major difference between the two studies, apart from overall improvements in neonatal care that took place during the interim, was the increased use of third generation cephalosporins. A follow-up study on the neonates from the 1985–7 study carried out when the children were 5 years old [1] revealed that 25.5% of the survivors suffered from serious disability, significantly more than among matched general practitioner (GP) controls. The question posed by the present study is to what extent the fall in acute phase mortality affected the incidence of serious disability.

Subjects and methods

The 256 survivors from the prospective national study of neonatal meningitis carried out in England and Wales between June 1996 and December 1997 are the subject of this 5-year follow-up investigation. In the original study, cases were identified prospectively and were included on the basis of an 'Intention to Treat' at the time of presentation. All neonates with signs and symptoms suggestive of meningitis and treated as such were recruited, including those who for various

reasons did not have a successful lumbar puncture. Ethical requirements dictated that the initial contact with the parents of index cases or controls had to be via the child's GP. Participating parents had then to give permission before information could be requested from the child's GP. To avoid the possibility of GP bias, controls matched for sex and age to the index case, were selected by the Health Authority from the same patient list as the index case. Hospital controls, additionally matched for gestational age and birth weight, were recruited from children who had been in the same neonatal unit and at the same time as the index case.

Parents and GPs of index cases and controls were asked to complete a questionnaire, based on that used previously [1], detailing any health or developmental problems in the areas of neuromotor development, learning, vision, hearing, speech and language, or behaviour and to indicate whether the child had a seizure disorder.

Using the same model [10] as in our previous study, children were allocated to one of four categories of disability (Table 1).

Data analysis

Differences between the meningitis group and the two control groups for the six parameters examined were determined using STATA software (version 8.2). Differences were tested with either the χ^2 or, when appropriate, Fisher's exact test. A legitimate use of Odds Ratios was done when necessary. The predictive power of a positive CSF culture in identifying future disability was assessed by calculating the 'Sensitivity' and 'Specificity'

Ethical approval

Ethical approval for the study was obtained from the London Multicentre Research Ethics Committee. Where the Local Research Ethics Committee did not accept this approval a full application had to be submitted to the Local Research Ethics Committee for the area in which each index case and control currently lived and to the Local Research Ethics Committee where the index cases and hospital controls had been originally treated.

Results

Of the 256 survivors from the national survey, 5 (2%) died within 27 months from causes related to meningitis; 15 could not be traced due to adoption, fostering, emigration, or for other reasons. In hindsight, the paediatrician concerned decided that the initial diagnosis of meningitis at the time of presentation was incorrect in four neonates. Completed questionnaires were received on 166 (72%) of the remaining 232 index cases, 109 GP controls and 191 hospital controls. None of the 66 'non-responders' had died by December 2001 (http://www.1837online.com). There were no significant demographic differences between the national cohort ($n=251$), the study population ($n=166$) and the 'non-participants' (66 non-responders + 15 lost to follow-up $=81$) (Table 2). The groups were very similar also with regard to clinical presentation, CSF culture results and the proportion of cases that had culture proven meningitis. The demographic details of the index cases ($n=166$) and the two sets of controls are shown in Table 3. The ethical constraints put upon this study and additional problems arising from the UK data protection legislation account for the differences in age between the index cases and GP controls.

Severe/moderate disability was reported in 23.5% of index cases and was statistically more common than in either GP (OR 16.4, 95%CI 4.1–142.7; χ^2 24.3; $P<0.0001$) or hospital controls (OR 3.9, 95%CI 2.0–8.1; χ^2 18.4; $P<0.0001$). None of the GP controls had severe disability (Table 4).

Differences in the educational needs and the frequency of cerebral palsy, neuromotor problems, hydrocephalus, epilepsy and hearing problems between the index cases and the two sets of controls are summarised in Table 5. Of the children at mainstream schools, 33 index cases, 11 GP controls and 25 hospital controls had special educational needs or required extra help. A 'Statement of Special Educational Needs' was significantly more common among Index cases than either GP controls (OR 4.9, 95%CI 1.1–45.4; Fischer's exact test (FET) $P<0.05$) or hospital controls (OR 3.4,

Table 1 Degrees of disability among index cases and controls [10]

Severe	Unable to attend a mainstream school. Multiple impairments/severe neuromotor/visual/auditory/or uncontrolled seizure disorders/significant intellectual impairment
Moderate	Impaired functioning but not associated with severe intellectual or developmental problems. Attended mainstream school who had: mild neuromotor disability/intellectual impairment/moderate sensorineural hearing loss/moderate visual impairment/controlled epilepsy or hydrocephalus without complications
Mild	Any condition prevalent among 5-year-old children but not typically associated with meningitis, e.g. middle ear disease, squint, febrile convulsions, behavioural problems
None	No evidence of any developmental problems

Table 2 Data of the national cohort of children who had neonatal meningitis in 1996–7 and the study population

	National cohort (n = 251)	Study population (n = 166)	Non-responders (n = 81)[a]
Demographic			
Male:female ratio	1.2	1.2	1.4
Gestational age (weeks)			
Mean (SD)	36.7 (4.2)	37.0 (4.2)	36.0 (4.4)
< 33 weeks	17%	15%	22%
Birth weight (g)			
Mean (SD)	2881 (903)	2935 (893)	2762 (929)
< 2000 g	17%	15%	21%
Age at diagnosis (days)			
Median	10.2	10.6	10.0
Clinical			
Coma (%)	6	7	2
Convulsions (%)	21	21	28
Rash (%)	8	4	3
Antibiotics within 48 h prior to diagnosis (%)	29	33	40
CSF culture			
Bacteria (%)	53	51	51
Viruses and yeasts (%)	8	9	8
Negative (%)	35	37	38
No CSF collected (%)	4	3	4

[a] 66 'non- responders' plus 15 lost to follow-up due to adoption etc

Table 3 Demographic data of the three groups of children

	Index cases (n = 166)	GP controls (n = 109)	Hospital controls (n = 191)
Gestational age (weeks) mean (SD)	37.0 (4.2)	39.2 (2.2)	36.4 (4.7)
Birth weight (g) mean (SD)	2930 (900)	3465 (505)	2821 (1078)
Sex ratio (M:F)	1.16	1.10	1.55
Age at follow-up (months) mean (SD)	63.4 (4.1)	69.3 (5.4)	63.4 (5.3)

Table 4 Degrees of disability in index cases and controls

	Index cases (n = 166)	GP controls (n = 109)	Hospital controls (n = 191)
Severe	9 (5%)	0	5 (2%)
Moderate	30 (18%)	2 (2%)	9 (5%)
Mild	43 (26%)	29 (27%)	57 (30%)
None	84 (51%)	87 (71%)	120 (63%)

95%CI 1.1–12.4; (FET) $P < 0.05$)[1] Cerebral palsy and hydrocephalus were both significantly more common among index cases than hospital controls (cerebral palsy: OR 3.7, 95%CI 1.2–13.3; χ^2 6.9; $P < 0.01$; hydrocephalus: OR 8.7, 95%CI 1.9–79.7; (FET) $P < 0.002$). In contrast, none of the GP controls were attending special schools and none had cerebral palsy, gross motor delay, hydrocephalus or sensorineural hearing loss.

All of the children with a conductive hearing loss were described, where specified, as 'mild' apart from one index case with a moderately severe hearing loss. No children were blind. The most common eye condition was squint in 19 (11%) index children, 12 (6%) hospital controls and five (5%) GP controls respectively ($P > 0.05$).

Behaviour problems were reported more frequently among index cases (63/166, 38%) than hospital controls (56/191, 27%) or GP controls (18/109, 17%). However, only six index cases, five hospital controls and three GP controls had behavioural problems that required professional help.

Children who had had a positive CSF culture during the acute phase accounted for 8/9 cases of severe disability and 23/30 cases of moderate disability, significantly more than those with negative CSF cultures or where CSF was not collected (OR 4.0, 95% CI 1.6–11.4; χ^2 10.1; $P < 0.002$) (Table 6). Among the eight children who had moderate/severe disability in the absence of a

[1] In England and Wales, children with special educational needs are assessed by a group of independent multi-professional examiners. Appropriate children are issued with 'A Statement of Special Educational Needs'. This is known as being 'Statemented'. Local Education Authorities are required by law to make appropriate special provision for such children.

Table 5 Educational needs and disability in index cases and controls

	Index cases (n = 166)	GP controls (n = 109)	Hospital controls (n = 191)
Schools attended:			
'Special schools'	8	0	5
Main stream schools:			
With extra help	14	8	17
'Special needs'	17	3	8
'Hearing needs'	2	0	0
Educated at home	0	1	1
Cerebral palsy	15	0	5
Hemiplegia	6 (2/6 + ataxia)		2
Diplegia	3		1
Quadriplegia	2		2
Other	4		0
Gross motor delay	4 (1/4 + ataxia)	0	0
Fine motor delay	0	1	3
Gross and fine motor delay	1	0	1
Hydrocephalus	14 (13/14 shunts)	0	2 (2/2 shunts)
Epilepsy	4	0	3
On medication	3/4	0	2/3
Febrile convulsions	1	2	0
Sensori-neural hearing loss	5 (1 severe, 4 moderate)	0	2 (1 moderate,1 mild)
Conductive hearing loss	22	9	14
No speech	2	0	2
Speech/language delay	38 (22%)	14 (13%)	35 (18%)

Table 6 Degree of disability in children who had culture-positive meningitis compared to those where no organism was isolated

CSF	Disability				
	None	Mild	Moderate	Severe	Total
Organism					
Bacteria	34	22	22	6	84
Group B streptococci	16	11	12	2	41
E. coli and other gram-negative bacilli	10	4	5	1	20
Viruses/yeasts	4	8	1	2	15
No CSF/no organism	46	13	7	1	67
Total	84	43	30	9	166

positive CSF culture, four had received antibiotics prior to lumbar puncture and three were too ill for CSF to be collected. Two had positive blood cultures (group B *Streptococcus* (GBS) and *Salmonella enteritidis*). Moderate/severe disability was reported in 14/41 (34%) of children who had had GBS meningitis, 6/20 (30%) who had had meningitis due to *E. coli* or other gram-negative bacilli and 35% where meningitis was due to other bacteria.

Discussion

No other studies on the long-term sequelae of neonatal meningitis are as large as ours, involve unselected cases or are based on national cohorts examined prospectively. The results of this study confirm our previous findings [1,8] that neonatal meningitis is associated with a high level of long-term morbidity. The degree of morbidity is significantly greater than in matched GP controls or in matched hospital controls that were in the neonatal unit with the index case for reasons other than meningitis. Predictably, hydrocephalus was significantly more common among meningitis cases than hospital controls ($P < 0.002$).

The study populations in this and the previous study [1] are essentially the same with regard to birth weight, gestational age, and the numbers of low birth weight and premature neonates.

In the earlier study there were significantly more cases of neuromotor problems (OR 1.9, 95% CI 1.0–3.7; χ^2 4.2; $P < 0.05$) and seizure disorders (OR 3.6, 95% CI 1.4–10.9; χ^2 9.0; $P < 0.005$). Also there were more laboratory confirmed cases, 70% compared to 60% in this study, and more cases due to *E. coli* (19%) than in this study (10%). *Haemophilus influenzae* was responsible for six cases in the first study and one in this. Despite these differences, the proportion of children with severe or moderate disability in the two studies is similar; 25.5% in the 1985–7 study compared to 23.5% in the present investigation (1996–7). This is noteworthy given that the acute phase mortality fell from 22% to 6.6%

during this 11-year period. The reported morbidity is comparable to the 23% sequelae reported in a retrospective study of 116 children in Australia [3]. Similar levels of long-term morbidity have been reported elsewhere in neonates [4,6] and older children [5].

Babies who had a negative CSF culture, as a result of receiving antibiotics before lumbar puncture, and those too ill to have CSF collected, complicate the prospective study of unselected populations. In our study, isolation of bacteria from the CSF was the best single predictor of long-term disability with a sensitivity of 81% and a specificity of 46%.

The degree of neuromotor disability and seizures reported in this study is lower than previously reported [1,8] (de Louvois unpublished information). The reasons for this are unclear and cannot be accounted for by any differences in the study groups. The level of sensorineural hearing loss among index cases in this study is also lower than that reported by us previously and that reported by other workers [2].

The acute phase mortality from neonatal meningitis in England and Wales fell dramatically between 1985–7 from 22% (25% in culture proven meningitis) to 6.6% (10% in culture proven meningitis) in 1996–7. This study has shown that the level of moderate/severe disability has not reduced in line with the drop in acute phase mortality; however, the smaller numbers of children with neuromotor disability or seizures is encouraging.

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