Changes in bacterial meningitis

P E Carter, S M Barclay, W H Galloway, G F Cole

Abstract

In 1964, one of us (WHG) undertook a retrospective study of bacterial meningitis in childhood in the north east of Scotland during the period 1946–61. We have recently carried out a similar review of cases occurring during 1971–86, to compare the incidence, mortality, and bacteriological patterns.

During the earlier period 285 cases occurred, a total incidence of 16.9/100 000 children per year. In the later period 274 children were affected, an annual incidence of 17.8/100 000. The overall mortality rate fell dramatically from 11.9% to 1.8%, the latter figure comparing favourably with recent published studies from Scandinavia and the United States.

There was a change in the bacteriological profile in the second period with a significant rise in cases due to *Haemophilus influenzae* at all ages. A fall in cases of meningococcal meningitis was significant in infants under 1 year of age only. Possible reasons for the change in the bacteriological pattern are discussed.

Bacterial meningitis remains one of the most common life threatening infections of childhood. Recent media reports highlighting local outbreaks or even single cases of meningococcal meningitis have raised public fears that Britain is suffering a major epidemic of the disease and that death is the expected outcome. There is, however, a paucity of British population based studies documenting the influence of improvement in social conditions, in antibiotic treatment, and in paediatric intensive care, on the incidence, mortality, and morbidity of bacterial meningitis. Similarly, little information is available about relative rates of infection by the three major organisms (meningococcus, *Haemophilus influenzae*, and pneumococcus) or age related susceptibilities. The only large scale study to include cases occurring during the last decade is that of Noah, based on laboratory reports rather than on hospital admissions and death notifications.¹

The north east of Scotland is well suited to population based studies as the catchment area is well defined and all seriously ill children are referred to Aberdeen for treatment. In an MD thesis published in 1964, one of us (WHG), described the experience of meningitis in this area during the period 1946–61.² Twenty five years later we have again studied the epidemiology of meningitis in the area and in this paper report changes in incidence and mortality, and in the pattern of infection.

Patients and methods

The Aberdeen catchment area is predominantly rural, consisting of the Grampian region and the Orkney and Shetland islands. The total population of the area (from census data) has risen from 483 374 in 1946 to 545 696 in 1986, probably related to the oil boom of the 1970s. In keeping with national trends, the average childhood population (0–12 years inclusive) has fallen from 104 803 during the period 1946–61 to 95 968 in the period 1971–86. Complete details for age distribution of the population were available only at 10 year intervals. For calculation of age specific rates, the numbers from the 1951 census were compared with the mean of figures from the 1971 and 1981 census figures, to obtain mid period values. Using these methods, in the former period 7.9% of children were aged under 1 year and 16.8% between 1–3 years. In the later period these figures were 7.5% and 14.7% respectively.

The first study consisted of a retrospective review of the case notes of all children in the area who developed bacterial meningitis between 1946–61. During this period children were treated in two paediatric units in Aberdeen and in the fever units of several rural hospitals. Records were gathered from all these sources. The number of undiagnosed cases resulting in death at home during this period is unknown. The study included infants under 4 weeks who became ill at home but not those still in the neonatal unit. The upper age limit was the 13th birthday. Infections complicating myelomeningocele were excluded. The results were reported in 1964.²

During the second study, to facilitate comparison, we duplicated the model of the first as closely as possible. The study was again retrospective, encompassed the same time interval of 16 years and extended between 1971–86. As before we included infants under 4 weeks affected at home, but not in the neonatal unit, and again the upper age limit was the 13th birthday. Before the second study there had been a change in regional policy so that all seriously ill children were referred to one of two Aberdeen paediatric units, and no children were managed in peripheral units. Infections complicating myelomeningocele or after neurosurgery were excluded. Two cases of sudden death at home due to bacterial meningitis were traced through forensic pathology records.

DIAGNOSTIC CRITERIA

In both studies children were included if a clinical diagnosis of bacterial meningitis was made

Royal Aberdeen
Children's Hospital,
Foresterhill,
Aberdeen AB9 2ZG

P E Carter
S M Barclay
W H Galloway
G F Cole

Correspondence to:
Dr Carter.

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and full antibiotic treatment given. Confirmatory criteria included: (a) organism grown from cerebrospinal fluid; (b) organism grown from blood with more than five white cells in the cerebrospinal fluid; (c) positive Gram stain or counterimmune electrophoresis on cerebrospinal fluid; (d) more than five white cells in cerebrospinal fluid where previous antibiotic treatment had been given; (e) sterile cerebrospinal fluid in the absence of previous antibiotic treatment but with one or more of: (i) cerebrospinal fluid polymorph count $>1000 \times 10^6/l$, (ii) protein concentration $>1000 \text{ mg/l}$, (iii) glucose concentrations $<1 \text{ mmol/l}$; and (f) meningeal inflammation at necropsy. Using these criteria, children with meningococcal septicaemia without meningitis were not included.

Results (see table)
1946-61

During this period 285 children developed meningitis, an annual incidence of 16.9/100 000 in children under 13 years. Thirty four children died, an overall case fatality rate of 11.9%. More boys were affected (57%) and more cases occurred in the colder months of December-May (64%). One hundred and thirty two cases (46% of the total) occurred in children under 1 year of whom 24 died (case fatality rate 18%).

1971-86

There were 274 children with bacterial meningitis during this period, an incidence rate of 17.8 cases/100 000 children per year. The total figures were not significantly different between the two periods. Again, more cases occurred during the winter (63%) and more boys were affected (59%). As before, children under 1 year were most affected (110 cases, 40% of the total). The only age group in which total incidence was significantly changed, however, was the 1-2 year group where there had been an appreciable rise (relative risk 1971-86: 1946-61 of 1.59; 95% confidence interval 1.16 to 2.17). The overall mortality rate of 1.8% included three children who died in hospital and two at home. Three deaths occurred in children under 1 year, a mortality rate of 2.8% in this age group.

MENINGOCOCCAL MENINGITIS
The total number of identified cases of menin-

Causes of bacterial meningitis 1946-61 and 1971-86

Organism	Period	Age in years			Total
		<1	1-2	3-12	
Meningococcus	1946-61	73 (8)	30 (2)	30 (3)	133 (13)
	1971-86	35 (1)	26	21	82 (1)
Haemophilus	1946-61	11 (3)	10	5 (2)	26 (5)
	1971-86	41 (1)	42 (1)	18 (1)	101 (3)
Pneumococcus	1946-61	11 (2)	8 (2)	12 (1)	31 (5)
	1971-86	13	0	4	17
Other known	1946-61	11 (7)	0	1	12 (7)
	1971-86	4 (1)	0	0	4 (1)
Unidentified	1946-61	26 (4)	23	34	83 (4)
	1971-86	16	20	34	70
Total	1946-61	132 (24)	71 (4)	82 (6)	285 (34)
	1971-86	109 (3)	88 (1)	77 (1)	274 (5)

Deaths are shown in parentheses.

gococcal meningitis fell strikingly from 133 in the first series (annual rate of 7.9/100 000 children) to 82 in the second study (annual attack rate of 5.3/100 000 children, relative risk 1971-86: 1946-61 of 0.69; 95% confidence interval 0.53 to 0.92). In the first series there were no local epidemic years, but during the second period there were two major peaks of infection as shown in fig 1. Thirteen deaths were found in the first series (case fatality rate of 10.3%) but in the second study only one (case fatality rate of 1.2%). The fall in the incidence of this condition was seen most dramatically in children under 1 year where the number of cases in the second study was half that of the earlier period (fig 2) (there was a relative risk 1971-86:1946-61 of 0.56; 95% confidence interval 0.38 to 0.85). The case fatality rate had fallen from 10.9% to 2.9% in infants under 1 year.

H INFLUENZAE MENINGITIS

When the two study periods were compared, it was evident that there had been a considerable rise in the incidence of bacterial meningitis because of *H influenzae*. During the period 1946-61 the number of cases was 26 (annual incidence rate 1.5/100 000 children), which increased to 101 (annual incidence rate 6.6/100 000 children) over 1971-86. As shown in fig 3, this trend had been exaggerated since 1975. Although there had been an increase in the disease across all age groups, the most pronounced age specific increase was in children between 1-3 years (relative risk 1971-86: 1946-61 of 5.26; 95% confidence interval 2.70 to 11.11). As shown in fig 4, this rise was closely

Figure 1 Cases of meningococcal meningitis 1971-86.

Figure 2 Age distribution of meningococcal meningitis 1946-61 and 1971-86.

Figure 3 Cases of *Haemophilus influenzae* meningitis 1971-86.

Figure 4 Age distribution of *Haemophilus influenzae* meningitis 1946-61 and 1971-86.

followed by that in children under 1 year (relative risk 1971-86:1946-61 of 4.35; 95% confidence interval 2.27 to 8.33). Although many more children were affected, deaths were fewer, the case fatality rate falling from 19.2% to 3%.

PNEUMOCOCCAL MENINGITIS

This remains the least common of the three major pathogens. Between the two periods the number of cases had fallen from 31 to 17, with most cases occurring in the first year of life or after open skull fracture. Because of the small numbers involved, age specific relative risks were not calculated.

OTHER ORGANISMS

Bacterial meningitis due to other organisms occurred mainly in young children, especially those under 3 months, and was associated with a high mortality. In both series Gram negative bacteria, particularly *Escherichia coli*, were the commonest organisms. Infections occurring in the neonatal unit were excluded. Consequently neonatal cases were under represented in the second study as during this period more babies were born in hospital. Again, numbers were too small for statistical interpretation.

UNIDENTIFIED ORGANISMS

A significant number of organisms were unidentified in both studies (28% in the first series and 25% in the second). Children in the area often

need to travel long distances to hospital and in those who are ill antibiotic treatment may be required before the journey. Other children were partially treated where the diagnosis had not been suspected. No figures were available for children who were given antibiotic treatment before lumbar puncture in the first study, but in the second more than half (54%) of the 'unidentified' group had received antibiotics compared with 39% where an organism was identified. Counterimmune electrophoresis became available in Aberdeen in 1982 and this has probably contributed to the lower figure for unidentified organisms in the second series. The changes in incidence were not significant.

Discussion

There has been no significant change in the incidence of bacterial meningitis in children in the Grampian region since 1946, but there have been significant changes in the pattern of infection and a dramatic fall in mortality. As the number of deaths outside hospital is unknown for the earlier period, it is likely that the true fall in mortality is even steeper. There are no recent British studies on defined populations in this age group available for comparison, but Goldacre reported a mortality rate of 10.9% in children under 10 in the north west metropolitan area between 1969 and 1973.³ Our mortality rate of under 2% compares favourably with more recent figures from other countries. A rate of 4% was reported in 1987 both by Valmari *et al* in Finland⁴ and Salwen *et al* in Sweden.⁵ An even lower mortality of 1.1% has been reported in a relatively small series from the United States.⁶ All the above series, however, considered only children who survived until hospital admission, unlike our group which includes deaths at home. It is likely that many factors have contributed to the reduced mortality including improved public awareness, earlier hospital referral, better nutritional state, improved antibiotic treatment, and greater skills in paediatric intensive care. In our own area management in central units by paediatricians rather than by general practitioners in country fever hospitals has probably made a major contribution.

Meningococcal meningitis appears to have declined in the north east of Scotland at a time when its prevalence has increased in some parts of Britain and Europe.^{7 8} Despite an overall fall in the attack rate of meningococcal meningitis in Grampian between 1971 and 1986, our figures do demonstrate two peak years in 1975 and 1985, which reflect the well documented national 'epidemic years'. Although these figures do not permit complacency, neither do they support the heightened public anxiety created by misinterpretation in local and national media.

The most striking finding in our study is the fourfold increase of meningitis due to *H influenzae* in the second period. This trend has been apparent since 1976 and *H influenzae* is now the commonest cause of bacterial meningitis in childhood in our region. The most noticeable increase has been in children under 3 years in

whom figures are similar to findings from Sweden where an annual incidence of 31/100 000 children under 5 is reported.⁹ It is this infection which is responsible for the increased total incidence rate in the 1–2 year olds, while in younger infants this is balanced by a fall in meningococcal infections. There has been much discussion in the recent literature of immunisation against *H influenzae*, and our figures would support the view that to provide maximum benefits a vaccine immunogenic under 6 months of age is necessary. Recent trials of conjugate vaccines in Finland¹⁰ and the United States¹¹ suggest that these vaccines confer protection even in early infancy.

Although *H influenzae* is believed to be the main cause of bacterial meningitis in children worldwide, the few available population defined studies suggest that, in Britain until 1980, meningococcus was the commonest causative pathogen. Goldacre's study of 730 cases showed meningococcal infection to account for 45% and *H influenzae* for 33% of the total.³ Similarly Davey *et al*, in a study of 635 cases in Birmingham between 1968 and 1977, reported that the meningococcus was the commonest organism in children and young adults.¹² Data resulting from notifications of diseases to the Communicable Disease Surveillance Centre (CDSC) during this period demonstrate that meningococcal meningitis was the most prevalent.¹³ Such data have to be interpreted with caution. A community based study in 1976 demonstrated that only 50% of cases of meningococcal, 17% of pneumococcal, and 11% of *H influenzae* meningitis were notified.¹⁴ Voluntary reporting from microbiology laboratories may provide a more reliable, although still incomplete, source of surveillance data. Noah quotes figures from the CDSC that indicate that reports of haemophilus meningitis have doubled since the early 1970s and by 1984 had become marginally more common than meningococcus in Scotland, averaged over all age groups.¹ The same trend was evident but less pronounced in England and Wales. Population defined studies are likely to be more sensitive in monitoring early trends in local disease.

A change in the pattern of infection in childhood meningitis began emerging in the United States in the late 1940s. Koch and colleagues in Los Angeles first drew attention to this when they reported a rise in the number of cases due to *H influenzae*, which began in 1945 and was sustained through to the end of their study period in 1960.¹⁵ Since this time a large number of studies have documented the increase in incidence of *H influenzae* and this organism has been firmly established as the major cause of the disease in the United States and Canada for the last three decades.^{16 17} The Australian experience has been similar.¹⁸ More recently the same changing profile of infection has been documented in some European countries. In Berlin the commonest cause of bacterial meningitis in patients admitted to the University Children's Hospital is *H influenzae*.¹⁹ In 1987 Salwen *et al* demonstrated a 150% increase in *H influenzae* meningitis in a defined Swedish population during the last 25 years.⁵

The strikingly increased incidence of *H influenzae* meningitis in Grampian is not easily explained. No evidence has been found that it is due to an increased referral rate to hospital, to improved laboratory methods, or to a change in age distribution. A number of interpretations are possible. It might be a phenomenon isolated in time and place and future studies may show a reversal of the current trend. This is perhaps unlikely in view of Noah's figures based on laboratory notifications from the whole of Britain showing a similar, if much less pronounced, trend.¹ Alternatively, it may indicate that the change in pattern of infection that emerged in North America 40 years ago is occurring in this country and Europe. The fact that similar findings have been documented in Scandinavia, a close geographical neighbour to the north east of Scotland, lends support to this view. Finally, it is possible that similar striking changes are occurring in other parts of Britain, but have been masked by local pockets of meningococcal infection influencing national studies.

Clearly further population based studies are required to clarify these possibilities.

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