

Long-term outcomes of childhood meningitis

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Meningitis and meningococcal disease remain a major source of anxiety to paediatricians and parents alike. Survival rates have improved with rapid diagnosis and appropriate management. However, survivors remain at risk of long-term neurodevelopmental sequelae.

There has been extensive research over the past 30 years into the outcomes of meningitis in childhood. This article reviews the publications relating to acute bacterial meningitis and meningococcal disease in childhood in developed countries. It is beyond the scope of this article to review tuberculous, fungal or viral meningitis.

Studies may be broadly divided into those looking at all bacterial meningitis and those which are organism specific.

GENERAL STUDIES

Baraff et al (1993) undertook a meta-analysis of results from 19 prospectively enrolled cohorts from developed countries published between 1976 and 1990. A total of 1602 children were included. Adverse outcomes were defined as an IQ ≤ 70 , spasticity or paresis in one or more limbs, seizures, or severe or profound hearing loss.

The results are summarized in *Table 1*. Overall mortality was 4.5%. Around 10% of the survivors suffered adverse outcomes as defined above. Organism-specific outcomes are shown in *Table 2*. From these data, pneumococcal

meningitis has the highest risk of mortality and long-term morbidity. Meningococcal meningitis appears to have the lowest risk of major sequelae compared with *Pneumococcus* and *Haemophilus* infections. This meta-analysis includes large numbers of patients and provides a comprehensive overview of major sequelae. It provides no information about more subtle neurodevelopmental problems which may follow meningitis.

Grimwood et al (1995) prospectively enrolled 158 survivors of childhood meningitis from the Royal Children's Hospital Melbourne between 1983 and 1986. One hundred and thirty (84%)

TABLE 1.
Outcomes of childhood meningitis: meta-analysis of 19 studies involving 1602 cases

| Outcome | Mean % of survivors |
|-----------------------------|---------------------|
| Profound mental retardation | 4.5 |
| Spasticity or paresis | 3.5 |
| Seizure disorder | 4.2 |
| Severe or profound deafness | 5.1 |

From Baraff et al (1993)

TABLE 2.
Organism-specific outcomes of meningitis: meta-analysis of 19 studies involving 1602 cases

| | <i>Haemophilus influenzae</i> | <i>Neisseria meningitidis</i> | <i>Streptococcus pneumoniae</i> |
|---------------------------------|-------------------------------|-------------------------------|---------------------------------|
| Mortality (%) | 3.8 | 7.5 | 15.3 |
| Number of cases | 1085 | 227 | 122 |
| Mental retardation (%) | 6.1 | 2.1 | 17 |
| Spasticity/paresis (%) | 5.1 | 2.1 | 11.5 |
| Seizures (%) | 6.1 | 1.4 | 14.3 |
| Profound or severe deafness (%) | 6.7 | Insufficient data | 15.5 |

From Baraff et al (1993)

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of this cohort were followed up at a mean of 6.7 years after initial illness. For each case, an age- and sex-matched control was recruited from the same school. Detailed assessments were performed by researchers blinded to the child's case or control status. Assessments included neurological examination, detailed neuropsychological assessment, audiology and behavioural questionnaires. Major sequelae were defined in a similar way to Baraff as IQ <70, spasticity, blindness, severe or profound deafness, epilepsy or a ventriculoperitoneal shunt. These were found in 8.5% of survivors, a similar proportion to other studies. However, detailed follow-up detected minor deficits in learning (IQ = 70–80), hearing and behaviour in a further 18.5% of the cohort.

Grimwood et al (1996) went on to study risk factors for adverse outcomes in this cohort. Multivariate analysis showed age <12 months, symptoms lasting >24 hours, seizures after 72 hours and focal neurological signs as independent risk factors. These were present in 95% of survivors with major sequelae but only in 37.5% with minor disabilities.

The majority of this cohort were re-examined 12 years after their initial illness (Grimwood et al, 2000). Many of the minor deficits seen at 7-year follow-up persisted through to 12 years, resulting in significant educational difficulties.

It should be noted that 76% of this cohort had suffered *Haemophilus* meningitis, with 14% and 5% having had *Pneumococcus* and *Neisseria meningitidis* meningitis respectively. This organism distribution is again similar to that in Baraff's meta-analysis and reflects the disease epidemiology before *Haemophilus influenzae* type b (Hib) immunization.

More recently, Bedford et al (2001) published data from a case-control study of 1584 survivors of meningitis in the first year of life. Based on Grimwood's work, these children would be at high risk of sequelae. The initial cohort was recruited between 1985 and 1987. Outcomes 5 years after initial illness were determined using GP and parental questionnaires. Children were

classified as having severe, moderate or mild disabilities. Severe disabilities prevented mainstream education; these included similar criteria to those used by Baraff and Grimwood. Moderate disabilities impair function but were not associated with severe intellectual or developmental impairment. They include mild neuro-motor disability, intellectual impairment, moderate hearing and visual impairment, well-controlled epilepsy and uncomplicated hydrocephalus. Mild disabilities included middle ear disease, febrile convulsion and behaviour problems. Severe impairments were found in 5.8% of survivors compared with 0.07% controls; 9.8% of survivors compared with 1.4% controls had moderate problems. Overall relative risk (RR) for moderate and severe problems was 10.33 (95% confidence interval (CI) = 6.6–16). There was a smaller increased risk of minor problems (29% cases vs 20% controls, RR = 1.47, 95% CI = 1.29–1.68).

Further analysis showed an increased risk of sequelae in neonates. Moderate to severe disability rates were higher following *Streptococcus pneumoniae* (24%) and group B *Streptococcus* (30%) infections compared with *Haemophilus* (10%) and meningococcal (9.5%) meningitis. It should be noted that in this study, only 26% of cases had confirmed *Haemophilus* infections compared with around 75% in Baraff and Grimwood. This factor and the differences in outcome measures may explain the differences shown in Table 3.

These studies broadly agree on the frequency of severe sequelae following childhood meningitis. The more recent studies have highlighted the incidence of subtle neurodevelopmental problems in children previously thought to have no sequelae. It must be noted that all of these studies recruited patients before routine Hib immunizations had been introduced. The epidemiology of childhood meningitis has since altered, with few *Haemophilus* infections occurring, and it is likely that incidence of sequelae has also changed. Each of these studies also highlights the differences in outcomes dependent on causative organism.

TABLE 3.
Differences in outcomes across three major studies

| | Baraff et al (1993) | Grimwood et al (1995) | Bedford et al (2001) |
|-------------------------|---------------------|-----------------------|----------------------|
| Recruited (years) | 1976–90 | 1983–86 | 1985–87 |
| Number of cases | 1602 | 130 | 1717 |
| Severe impairment (%) | 10 | 8.5 | 5.8 |
| Moderate impairment (%) | – | – | 9.8 |
| Mild impairment (%) | – | 18.5 | 29 |

Clinically, it is more appropriate to consider outcomes following specific infections rather than after meningitis as a whole.

ORGANISM-SPECIFIC STUDIES

Streptococcus pneumoniae

Pikis et al (1996) studied 47 survivors of childhood pneumococcal meningitis between 1967 and 1988 from Thessaloniki. Of these cases, 20% were found to have mental retardation, 15% had a seizure disorder, 17% had hearing loss and 2% had visual and behavioural impairments. Thirty per cent had at least one neurological handicap. Mortality in this cohort was 18%. This study includes only small numbers recruited over a long time period, and only major sequelae were included.

Kornelisse et al (1995) published a similar series of 83 cases over 24 years from 1970. Mortality (17%), neurological sequelae (25%) and hearing loss (19%) were similar to the Greek study.

Results of a multicentre 3-year (1993–96) surveillance of pneumococcal meningitis across eight US children's hospitals were published in 1998 (Arditi et al, 1998). One hundred and eighty children were recruited. Mortality was 7.7%. Adverse outcomes were defined as neurological sequelae and/or sensorineural deafness at hospital discharge. Overall, 25% of survivors had evidence of neurological sequelae at discharge, including spasticity, ataxia, cranial nerve dysfunction, cortical blindness, vegetative state and hydrocephalus; 32% of survivors suffered unilateral (17%) or bilateral (15%) moderate to severe hearing loss at discharge.

These three studies demonstrate high mortality and major sequelae following these infections. The low incidence of pneumococcal meningitis makes recruitment of large cohorts difficult. There is a need for a large multicentre prospective outcome study including a control population. It is likely that, in addition to major sequelae, survivors may also be at risk of subtle neurological deficits.

Haemophilus influenzae

Taylor and colleagues have done the most extensive work on outcomes following *Haemophilus* meningitis in childhood.

In an initial small study (Taylor et al, 1984), 24 cases between 1973 and 1975 were assessed 7 years after initial illness. Compared with sibling controls, only subtle differences were found on psychometric testing, and it was concluded that prognosis may be better than previously documented.

A larger study with a cohort of 97 children presenting in Canada between 1972 and 1984 was later published (Taylor et al, 1990). Fourteen (14%) of the cohort suffered long-term neurological sequelae. Eleven of these suffered hearing loss, of which five cases were bilateral severe to profound hearing loss, and the remainder were unilateral or mild. Two patients suffered with seizure disorders, and one had hemiplegia and severe learning difficulties. Overall, severe sequelae were found in around 7% of survivors. This figure is similar to those found in the general meningitis studies of Baraff and Grimwood, whose cohorts were mainly *Haemophilus* survivors. This study again found additional subtle differences between cases and sibling controls on psychometric and behavioural testing. Sequelae were found to be higher in those who had suffered acute neurological complications, such as seizures or coma (Taylor et al, 1998).

Haemophilus meningitis has become uncommon in the UK since the introduction of *H. influenzae* vaccine in 1992.

Meningococcal disease

Meningococcal disease in childhood may be classified on clinical and laboratory grounds into septicaemia (30%), meningitis (10%) or mixed disease (60%). It is likely that all survivors of meningococcal disease may be at risk of long-term sequelae. Seventy per cent of cases have meningitis as part of their illness and are therefore at risk of neurodevelopmental sequelae by analogy with the data above. Septicaemic cases may not have features of meningitis, but 30% of these have a fulminant illness involving hypotension and coagulopathy and require paediatric intensive care unit (PICU) management. This confers a risk of sequelae on these survivors. Compared with other organisms, there has been relatively little research into outcomes in meningococcal disease. The terminology has also been clarified only in recent years, and many older studies included septicaemic children under the heading meningitis.

Moss (1982) assessed 60 survivors from the outbreak in Bolton in the early 1970s. This cohort had suffered a high mortality of 17%. He found no significant differences on detailed neurological examination or on psychometric assessment; 5% of cases showed unilateral sensorineural deafness. These data are not likely to be relevant now. There have also been changes in classification and epidemiology of meningococcal disease together with advances in PICU management.

The authors' group has recently published data on a cohort of 152 cases of childhood

meningococcal disease on Merseyside between 1988 and 1990 (Fellick et al, 2001). These were prospectively recruited into an acute study, and detailed clinical and laboratory information was collected; 139 cases survived. Between 1998 and 2000, 115 (83%) survivors took part in a detailed follow-up study. Tests of motor skills, cognitive function, behaviour and hearing were applied to both survivors and a population of age- and sex-matched controls. Subjects were classified as having severe, moderate or mild impairments based on similar criteria to other studies. Based on these criteria, four cases (3.5%) and no controls had major impairments. Eighteen cases (15.7%) and five controls (4.3%) had moderate problems (adjusted odds ratio = 3.6, 95% CI = 1.3–10.3). Twenty-two cases and 14 controls had one or more minor problems (adjusted odds ratio = 1.6, 95% CI = 0.8–3.4).

The follow-up group was divided into cases of meningitis (16), septicaemia (37) or mixed disease (72). The cases with moderate and severe impairments problems were distributed between the three diagnostic groups with no significant differences. However, survivors of pure meningitis were at greater risk of minor sequelae.

CONCLUSIONS

Following bacterial meningitis, severe neurodevelopmental sequelae are found in 7–10% of survivors. Minor but educationally significant deficits are found in up to 20%. Subjects with neurological complications during the acute illness are at increased risk of long-term sequelae. Pneumococcal infections have a higher incidence of severe sequelae when compared with meningococcal or *Haemophilus* infections.

The most recent study reviewed in this article stopped recruiting in 1990. Advances continue to be made in PICU management which may improve survival at the expense of sequelae. There have also been significant changes in epidemiology following successful immunization campaigns for Hib and group C meningococcus. It is important that these sequelae continue to be monitored and documented by means of prospective controlled studies. Group B meningococcal and pneumococcal infections remain the main challenges.

Clinicians should continue to distinguish between pure meningitis and cases with septicaemia on the basis of clinical and laboratory data. Not only is the acute management different for septicaemia and meningitis, but both acute and long-term outcomes for these conditions differ significantly.

Follow-up guidelines have not been standardized. All survivors of meningitis and meningococcal septicaemia should have a detailed audiology assessment as soon as possible after recovery. Those at risk of severe sequelae are mostly apparent during hospital admission, and early referral to child development teams is advised. Clinicians and parents should be aware of the risks of subtle neurodevelopmental sequelae, which may only emerge in the school years. Routine screening for these problems would be time-consuming and have a low yield in comparison with parental and school awareness. **HM**

Conflict of interest: none.

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KEY POINTS

- Major neurodevelopmental sequelae are seen in 7–10% of survivors of meningitis, and minor sequelae in a further 20%.
- The outcome is dependent on the causative organism and is worst for *Streptococcus pneumoniae*.
- Epidemiology and treatments are changing rapidly. Outcomes should be monitored with prospective controlled studies.
- Clinicians should distinguish between meningitis and septicaemia, as the acute and long-term outcomes differ significantly.