The impact of new diagnostic methodologies in the management of meningitis in adults at a teaching hospital

D.R. CHADWICK and A.M.L. LEVER

From the Department of Infectious Diseases, Addenbrooke’s Hospital, Cambridge, UK

Received 30 January 2002 and in revised form 3 July 2002

Summary

Background: Suspected meningitis is a frequent reason for admission to hospital in the UK. While bacterial meningitis requires prompt antibiotic therapy to reduce mortality and morbidity, enteroviral meningitis, the most frequent viral cause, is almost invariably a benign disease.

Aim: To determine the clinical presentation, laboratory findings and outcome of meningitis by microbiological aetiology and patient age, and to assess the clinical management of adults presenting with meningitis, with reference to national guidelines.

Design: Retrospective case-note review.

Methods: Adult (>14 years) admissions to Addenbrooke’s Hospital with meningitis or meningococcal septicaemia March 1996–September 2001 were audited retrospectively. The case definition was: symptoms compatible with meningitis, and either abnormal CSF (leukocytes >5x10⁹/ml) or meningococcal disease. The only exclusion criterion was the presence of a ventricular shunt.

Results: Only 30% of patients seen by a General Practitioner were given pre-admission antibiotics. In a substantial number of cases, including those with bacterial meningitis, antibiotic administration was delayed either because patients were sent for CT head scans (delaying a lumbar puncture) or because the diagnosis was not considered, especially in elderly patients with reduced conscious levels. There were no confirmed cases of H. influenzae meningitis. Overall outcomes in terms of mortality and disability were similar to UK national data. A surprising number of patients (40%) were afebrile on admission.

Discussion: The proportion of patients with meningitis given pre-hospital antibiotics by GPs is still worryingly low, although early hospital management has improved. Improved diagnostic facilities, particularly viral PCR assays, reduce antibiotic usage and hospital stay, with considerable financial savings.

Introduction

Bacterial meningitis is one of the most serious causes for admission to hospitals in the UK, requiring prompt administration of antibiotics, which has been associated with decreased mortality in previous studies. Its estimated incidence is around 1500 cases/year in the UK, with a mortality of 8–10% in meningococcal infection. With greater sophistication in the diagnosis of organisms causing meningitis, particularly with the application of PCR technology for viral and meningococcal meningitis, it has been possible to establish the cause of meningitis in an increasing proportion of admissions, enabling comparisons of clinical and laboratory parameters in different types of meningitis. Furthermore, it has become apparent both in this hospital and over the entire UK over recent years that there have been summer epidemics of enteroviral meningitis, due to echovirus types 13

Address correspondence to Dr D.R. Chadwick, Department of Infectious Diseases, Addenbrooke’s Hospital, Cambridge CB2 2QQ. e-mail: david.chadwick@addenbrookes.nhs.uk

© Association of Physicians 2002
and 30.5,6 This form of meningitis, while sometimes causing considerable morbidity, is associated with negligible mortality in adults, and rapid diagnosis may reduce hospital stays and antibiotic usage.

Management guidelines for meningitis published over the past few years have emphasized the importance of early (including pre-hospital) antibiotic treatment for cases of suspected meningitis, in addition to other recommendations regarding appropriate investigations and prophylaxis.7 In a previous study of the early management of meningitis patients admitted to this hospital, General Practitioners (GPs) frequently had not given antibiotics to patients with suspected meningitis before admission, and in a significant number of cases, there were delays in receiving antibiotics after hospital admission, possibly related to the desire to obtain cerebrospinal fluid (CSF) by lumbar puncture before giving antibiotics. One recommendation regarding investigation is that a CT head scan is only performed prior to lumbar puncture if there is focal neurological impairment or a reduced consciousness level, papilloedema, previous brain pathology, or the patient is immunosuppressed.7,9 A recent study of several hundred patients with suspected meningitis in the USA confirmed that patients with none of these features were at negligible risk of complications of a lumbar puncture.10 Our experience has been that this recommendation is frequently ignored, and a large number of patients with suspected meningitis have a CT scan inappropriately, possibly due to the desire to exclude raised intracranial pressure prior to performing a lumbar puncture. In some cases, obtaining a CT scan has delayed the diagnosis of meningitis and administration of antibiotics.

This retrospective study attempted to determine the clinical presentation, laboratory findings and outcome of meningitis according to aetiology of meningitis, and to assess the clinical management of meningitis with reference to national guidelines. Most published studies of meningitis have not been undertaken in solely adult populations: in this paper we describe findings in an exclusively adult cohort.

Methods

Using a combination of clinical coding data, ward admission logs, data from the Addenbrooke’s Hospital Clinical Microbiology and Public Health Laboratory Service and notifications from the Cambridgeshire Health Authority, adult admissions to Addenbrooke’s Hospital with meningitis or meningococcal septicaemia between March 1996 and September 2001 were catalogued. Patients’ case-notes were reviewed, and those fitting the case definition were audited retrospectively. The case definition was: any patient aged over 14 years with symptoms compatible with meningitis, and either abnormal CSF (leukocytes > 5 x 10⁹/ml) or meningococcal disease. Accepted microbiological definitions for meningococcal disease included positive Gram stains (CSF/skin scrapings), cultures, PCR or serology. The only exclusion criterion was the presence of a ventricular shunt. Clinical, epidemiological and laboratory information, from case notes, hospital information systems and the Cambridgeshire Consultant in Communicable Disease Control (CCDC), was compiled and analysed (including comparisons with reference to age and aetiology of meningitis) using Microsoft Excel. Statistical analysis consisted of comparison by two-way analysis using the χ² test for categorical variables, or the unpaired t-test for mean estimates of continuous variables. The study was approved by the sub-committee of the Addenbrooke’s NHS Trust Clinical Audit Department.

Results

A total of 116 cases of meningitis or meningococcal septicaemia were identified. These were divided into meningococcal meningitis/septicaemia (32), bacterial meningitis due to other organisms (8), enteroviral meningitis (28), viral meningitis due to other organisms (8) and undiagnosed (40). Approximately 30–40% of the undiagnosed cases were likely to have been bacterial meningitis on the basis of high CSF cell counts and protein levels, and high inflammatory markers. Non-meningococcal bacterial cases were mostly due to S. pneumoniae (the remainder being other streptococci), whilst non-enteroviral viral meningitis cases were equally split between herpes simplex virus (HSV) and varicella zoster virus (VZV) meningitis.

Epidemiological data is illustrated in Figure 1. More females (57%) than males (43%) were admitted with meningitis, and this distribution did not differ significantly according to aetiology of meningitis. Most cases (52%) occurred in patients aged between 15 and 30 years, and there were progressively fewer cases in the older age groups. It was notable that there were no cases of confirmed viral meningitis in patients over 65 years. There were also significantly more cases of viral than bacterial meningitis in the 30–45 year age group. Figure 1b shows co-existing diseases, possibly predisposing to meningitis in the patients surveyed. Less than 25% of all cases had any predisposing condition.
Figure 2 shows differences in clinical presentation between patients according to age and underlying cause of meningitis. Older patients (age > 45 years) were less likely to present with meningism (particularly photophobia or vomiting), but were much more likely to be obtunded with a reduced Glasgow Coma Scale (GCS) score (Figure 2a). The only significant differences between viral and bacterial meningitis (Figure 2b) was that patients with viral infection were more likely to have photophobia and very unlikely to have either a rash or a reduced conscious level on admission. The clinical features of the two groups did not otherwise differ. Nearly 40% of all patients were afebrile at presentation, which was particularly the case in young patients with viral meningitis. There was no difference in the incubation period of the illness related to patient age or to the aetiology of meningitis.

The clinical management of meningitis with reference to antibiotic therapy is illustrated in Figure 3. Of all patients who were seen by a GP prior to admission, only 30% were clearly documented as having been given antibiotics (Figure 3a). This figure rose to 40% of cases with confirmed meningococcal infection, but was around 20% for those with viral meningitis. Of the four cases of bacterial meningitis who subsequently died, all of had been seen by GPs, but none had received pre-admission antibiotics. GPs referral letters commonly noted that the diagnosis of meningitis was suspected (indeed this was the reason for admission in almost all of the cases), however there was often no mention of pre-admission antibiotics having been given in the letter or subsequent case notes. The duration between arrival in hospital and receipt of the first dose of intravenous antibiotic is shown in Figures 3b and 3c. The median time between arrival and first antibiotic dose was around 90 min for all cases, and also for viral meningitis cases. This was significantly shorter (49 min) for meningococcal infection. Cases of non-meningococcal bacterial meningitis were treated much less swiftly (180 min), as were undiagnosed cases (174 min). This was also mirrored by the proportion of cases that received antibiotics within 1 h of arrival, which amounted to almost 70% of cases with meningococcal infection, but only 25–35% for other cases. Overall, 42% of admissions received antibiotics within 1 h. While most cases were given antibiotics before having a lumbar puncture or CT head scan, in a significant number of cases, in particular 4 of the 8 with non-meningococcal bacterial meningitis, administration of antibiotics was delayed because of these investigations.

The commonest antibiotic used was cefotaxime (84%); benzyl penicillin alone was used in 6% of cases (all either meningococcal or pneumococcal infections), and the remaining patients received combinations of these antibiotics. The mean duration of antibiotic therapy was 5.1 days for all cases reviewed: 5.6 days for those with bacterial meningitis, and 3.2 days for those with viral meningitis. The reviewers felt that the antibiotic received was appropriate in 96% of all cases, although the dose of cefotaxime prescribed initially was frequently lower than that recommended for meningitis. The median duration of admission was 5 days for all cases; patients with bacterial meningitis stayed for a median of 7 days, while those with viral meningitis had a median stay of 4 days. Antibiotic prophylaxis of patients with confirmed or suspected meningococcal infection to eradicate carriage of meningococcus in the patient’s upper respiratory tract was administered in 74% of all cases reviewed. We were unable to audit the rate and mode of administration of prophylaxis given to close contacts of the patients (via the CCDC) with our available resources. The mode of prophylaxis (ciprofloxacin or rifampicin) given in different...
types of meningitis is illustrated in Figure 4. Ciprofloxacin was used most commonly for prophylaxis in all types of meningitis. Of those with proven meningococcal disease, only 3% were not given any prophylaxis, and about three-quarters of all these patients were given ciprofloxacin. A high proportion (92%) of patients with non-meningococcal bacterial meningitis also received prophylaxis, again most commonly ciprofloxacin. Around 60% of cases with viral or ‘undiagnosed’ meningitis received some form of prophylaxis.

Information on notifications of patients to the CCDC was only available from 1996 to 2000. Of the cases reviewed during this period, 64% were notified. The final outcome of the cases reviewed, in terms of survival or neurological disability, is shown in Figure 5. The mortality of all cases reviewed was 7%; this was similar in patients with meningitis or septicaemia. Few patients suffered any long-term neurological impairment due to meningitis. Those who did more often had bacterial meningitis (14%) and were over-represented in the older patients (16%). Only one patient with confirmed viral meningitis suffered any long-term impairment, this patient having HSV-1 meningitis; 9% of patients with meningococcal infection were estimated to have suffered neurological complications.

The proportion of patients having CT head scans on admission, and the results and influence of the scan are illustrated in Figure 6. Two-thirds of all patients had a scan, and approximately 70% of patients with bacterial meningitis were scanned, while 47% of those with viral meningitis were scanned. Overall, a CT scan was thought to be appropriate by the reviewers in only 45% of these cases. While a considerably lower proportion of cases than this actually satisfied the criteria for a CT scan, as outlined earlier, it was felt that in a significant proportion of these cases a CT was warranted due to the sudden onset of headache, for exclusion of subarachnoid haemorrhage. Perhaps
surprisingly, there were no intracranial abscesses detected in cases of bacterial meningitis on scanning. We also felt that the decision to perform a CT scan significantly and unnecessarily delayed the administration of antibiotics in around 30% of all cases scanned. In most cases this appeared to be consequent on the diagnosis of meningitis not being seriously considered. Lumbar puncture was delayed because of the wait for a CT scan to be performed, and for the result to become available.

CSF results were substantially different according to the cause of meningitis. Average polymorph numbers were much higher in patients with bacterial meningitis, as would be expected, while lymphocyte numbers were similar in both groups. Interestingly, in viral meningitis (mostly enteroviral in aetiology) lymphocyte levels were not significantly higher than polymorph levels, with a substantial proportion of patients having more polymorphs than lymphocytes. Calculation of median numbers of cells in each group actually showed more polymorphs than lymphocytes (21 vs. 16) in viral meningitis, although the difference in median numbers in bacterial meningitis (845 vs. 10) was more pronounced (data not shown). We found that CSF protein and glucose levels were more orthodox in bacterial and viral meningitis, with patients having lower glucose levels (and lower CSF:serum ratios), as well as higher protein levels in bacterial meningitis. Blood results on admission were also not unexpected, showing that patients with bacterial meningitis had a substantially higher white cell count, C-reactive protein (CRP) level and erythrocyte sedimentation rate (ESRs) than patients with viral meningitis.

**Discussion**

This study was primarily conducted in order to assess the medical management of meningitis patients presenting to Addenbrooke's Hospital with the availability of sophisticated new diagnostic technologies. Secondary assessments were principally the clinical presentation, outcome and laboratory features with reference to aetiology of meningitis and/or age of the patients. In contrast to most recent reports looking at the presentation and management of meningitis, this review was conducted solely in adults. The completeness of case ascertainment was felt to be adequate given the multiple sources used for identifying cases of
meningitis, although it is possible a few patients, particularly critically-ill cases (including deaths), were missed due to miscoding of patients on medical wards or the Intensive Care Unit. Evidence of miscoding of meningitis cases in the hospital was substantiated by the few patients who were solely identified from notifications to the CCDC. Meningococcal septicaemia cases were included in this study since the management is virtually identical to that of meningitis, and it would be expected that a significant proportion of these cases would have had meningitis; however, to confirm this by obtaining CSF samples is unnecessary. The ability to make a microbiological diagnosis in such a high proportion of cases was principally due to the availability and performance of CSF PCR assays for viruses (performed by the CPHLS) and meningococcus (Manchester PHLS), as well as routine microbiological assays. The epidemiological features were typical of cases in the UK as a whole, and similar to those recently reported; in particular, the proportion of cases with enteroviral meningitis was consistent with national data. The absence of any confirmed cases of *H. influenzae* meningitis was notable, possibly suggesting reduced transmission from children following the introduction of the Hib vaccine.

The medical management of cases of meningitis has attracted considerable scrutiny over recent years, with a number of reports raising concern in several areas of management of bacterial meningitis in the UK. These studies showed that only around 13–30% of patients with bacterial meningitis were given pre-admission antibiotics. Despite the difficulty in ascertaining whether a patient actually received pre-admission antibiotics from case notes, the finding that only 30% of patients in this study definitely received them is a significant cause for concern, as was the fact that none of the four patients who ultimately died (and were seen by GPs) received pre-admission antibiotics. We frequently saw admission letters sent by GPs describing meningism and fever as well as querying the possibility of meningitis, whilst failing to document administration of antibiotics, suggesting a continuing widespread ignorance of the importance of administering antibiotics in cases of suspected bacterial meningitis, and a failure of penetration of guidance from the Chief Medical Officer to General Practitioners. The fact that there were very few differences in the initial presentation of viral and bacterial meningitis in this study underlines the difficulty in distinguishing between these infections clinically, reinforcing the need to treat any suspected meningitis as if it were potentially bacterial.
Since the proportion of patients receiving pre-admission antibiotics by GPs has remained largely unchanged over the past decade,\(^4,8,12\) there is clearly a need to seek new ways to reinforce the message of the importance and urgency of antibiotic administration pre-admission as, on the basis of this survey, current measures have failed.

The speed of administration of antibiotics on arrival in hospital varied considerably according to the cause of meningitis. The relative rapidity with which patients with suspected meningococcal meningitis were given antibiotics is probably accounted for by their being younger and more unwell than other cases. The finding that 70% of these cases were given antibiotics within 1 h was felt to be satisfactory, and is consistent with performance in other UK hospitals.\(^4\) Of greater concern, however, was the speed at which patients with other types of bacterial meningitis, or undiagnosed cases received treatment. While many of these cases received antibiotics promptly, the median time of 3 h was much longer, owing to a substantial minority who waited in >6 h (several >48 h). In these patients, it was apparent that the diagnosis of meningitis was not seriously considered on admission, despite their symptoms consistent with meningitis and often being febrile. There appear to be two main reasons for the delay. First, particularly in older patients, cases who presented with reduced conscious levels were not thought likely to have meningitis until other causes (e.g. cerebrovascular accident) had been excluded, prompting a lumbar puncture. Second, in many patients the decision to perform a CT head scan prior to a lumbar puncture (and then deciding whether to give antibiotics) was clearly a common mode of decision-making. This led to a significant delay in giving antibiotics in around 30% of all patients scanned, a clearly avoidable delay. Delays in diagnosis have been associated with increased mortality in several studies.\(^3,13,14\) In our study, these patients were more frequently afebrile on admission, although still complaining of headaches, perhaps making the diagnosis of meningitis less likely initially. It was clear from our cohort, as was also noted in two recent reports,\(^9,10\) that too many patients were being scanned on admission. While several abnormalities were found in patients who probably did not warrant a CT scan, none is likely to have jeopardized the patient had a lumbar puncture been performed, nor would it have changed subsequent management. Furthermore, in many of the 55% of cases where a scan was not warranted, a lumbar puncture would almost certainly have been performed sooner and antibiotics started more quickly. One encouraging finding was that the vast majority of patients did receive antibiotics prior to lumbar puncture, a definite improvement compared to the review from the early 1990s in the same hospital.\(^8\)

The type and duration of antibiotics given were appropriate in virtually all cases. Compared to the earlier review,\(^8\) more patients received cefotaxime compared to benzylpenicillin, and there was a trend towards a shorter duration of therapy, probably due to increasing diagnosis of enteroviral meningitis. In these cases it was frequently possible to stop antibiotics and discharge the patient after two or three days as a result of this diagnostic service. It was estimated in our hospital that reduced antibiotic and bed usage led to a cost saving of around £8700 per year in 2000–2001. Had enteroviral PCR tests been available within 24–36 h of admission (as a daily or ‘on-call’ service), enabling earlier discharge of patients with confirmed viral meningitis, it is estimated that this cost saving would have exceeded £13 000 per year. Assuming similar savings could be made in other UK hospitals, using data from reports of enteroviral meningitis in England and Wales in 2001,\(^6\) this diagnostic tool would lead to a total saving to the NHS of approximately £256 000 per year if cases of enteroviral meningitis were confirmed within 36 h of admission. Clearly, even greater savings would be made if paediatric cases were included in this analysis.

Administration of prophylaxis was also felt to be largely appropriate, with almost all cases of bacterial meningitis receiving suitable prophylactic ciprofloxacin, or occasionally rifampicin. Once again, increased awareness and diagnosis of enteroviral meningitis led to a trend towards reduced use of prophylaxis in family members where CSF findings were characteristic and inflammatory markers not greatly raised, reducing levels of anxiety in contacts and family members. The clinical outcome for admissions was largely predictable, with a mortality of 12% for bacterial meningitis as a whole and 6% for meningococcal infection, the latter similar to national data.\(^8\) The mortality for older patients with bacterial meningitis compared favourably to other published studies in this age group.\(^14,15\)

The comparison of clinical presentation and laboratory features with respect to age and type of meningitis found that in common with other studies,\(^14–16\) older patients were more likely to present atypically with reduced conscious levels, confusion and less frequently with headaches. Interestingly, patients with viral meningitis more
commonly presented with photophobia than those with bacterial meningitis, which is not frequently recognized as being a specific feature of viral meningitis. Also of interest was the observation that a significant proportion of patients were afebrile at presentation. Laboratory data was largely compatible with standard definitions for different types of meningitis, but the fact that the number of CSF lymphocytes did not generally exceed those of polymorphs in viral meningitis was unexpected, although it has also been noted in children with enteroviral meningitis.17 The CRP, ESR and white cell count were all good predictors of whether the patient would have bacterial or viral meningitis, each being significantly higher in bacterial meningitis.

The findings of this study have led to several recommendations in order to improve the management of meningitis locally. GPs have been reminded, through a local Microbiology newsletter, of the importance of giving pre-hospital antibiotics in all cases of suspected meningitis. Junior doctors have been reminded of recommendations to administer antibiotics promptly on admission in these cases, and to avoid unnecessary CT head scans. Finally, the local PHLS is in negotiation with the Trust to provide funding for daily PCR assays to identify patients with viral meningitis more rapidly, with the aim of reducing hospital stay and expenditure on antibiotics.

Acknowledgements
We thank the Addenbrooke’s Hospital Clinical Microbiology and PHLS for providing diagnostic services including viral PCR assays, as well as the Addenbrooke’s Hospital Department of Clinical Audit for providing case notes.

References