Med. J. Malaysia Vol. XXXII No. 2, December, 1977

Purulent meningitis in childhood

by *Lee, E. L.*
M.Med.(Paed.), F.R.A.C.P.

Puthucheary, S. D.
Dip. Bact.,

Khoo, B. H.
F.A.A.P., M.R.C.P.(U.K.), M.Sc.(Lond.), D.T.M. & H., D.C.H.

and *Thong, M. L.*
Dip. Bact.

Department of Paediatrics and Medical Microbiology,
University of Malaya, Kuala Lumpur.

Introduction

SPECIFIC ANTIMICROBIAL THERAPY has dramatically improved the outcome in bacterial meningitis. However, mortality and morbidity rates for this infection are still considerable (Fraser *et al.*, 1973; Dawson and Hammond, 1976; Public Health Lab. Service, 1974). Children with purulent meningitis in developing countries are reported to have a less favourable outcome compared to those from the industrialised nations (Seriki, 1970). The reasons for this are not clear and there is little published data on this serious infection in the local community. This is a study of pyogenic meningitis in infants and children admitted to the University Hospital, Kuala Lumpur, during the period between June 1970 and June 1977. Our experience with neonatal bacterial meningitis, where there are special problems in diagnosis and management, has been reported elsewhere (Lee *et al.*, 1977) and will be omitted from this review.

Study Population

All children between the ages of one month and twelve years admitted to the Paediatric Unit of the University Hospital during the 7-year period were included in the study if analysis of the cerebrospinal fluid (CSF) revealed a minimum of three of the following findings:

1. leukocyte count $\geqslant 100$ cells per cu.mm;
2. sugar $\leqslant 50$ mg per 100 ml;
3. protein $\geqslant 50$ mg per 100 ml;
4. positive direct smear for micro-organisms;
5. positive bacteriological culture.

Patients with meningitis caused by *Mycobacterium tuberculosis* were excluded. Fifty-nine patients fulfilled the above criteria and their records were reviewed.

Clinical Features

A breakdown of the major symptoms and signs is presented in Table I.

Table I
Frequency of Clinical Findings among 59 Children with Purulent Meningitis

Male sex	...	...	38 (64.4%)
Female sex	...	...	21 (35.6%)
Fever	...	...	58 (98.3%)
Anorexia	...	...	51 (86.4%)
Convulsion	...	...	46 (80.0%)
Listlessness	...	...	35 (59.3%)
Irritability	...	...	23 (39.0%)
Vomiting	...	...	21 (33.8%)
Headache	...	...	6 (10.1%)
Neck stiffness	...	...	37 (62.7%)
Tense fontanelle	...	...	29 (49.1%)
Kernig's sign	...	...	16 (27.1%)
Semicoma/coma	...	...	13 (22.0%)
Focal neurological deficit	...	...	9 (15.1%)
Opisthotonus	...	...	4 (6.8%)
Skin rash	...	...	1 (1.7%)

There was a male preponderance and 73% of the patients were below 12 months of age at presentation. The duration of symptoms before diagnosis ranged from 1 to 7 days (mean 3.7 days). The most consistent complaints were fever, anorexia, listlessness and irritability. The latter was often described by the mother as resentment on the part of the child to being handled or nursed, contrary to its normal behaviour. Convulsions were present in 80% of the patients during the course of the illness but was the presenting symptom in less than 30 percent. A bulging fontanelle was so impressive in some young infants that a few observant mothers commented upon this point in the history. In children above 2 years of age, vomiting and headache were additional features. Symptoms suggestive of respiratory infection were the initial complaints in about 45% of the cases and these frequently caused a delay in diagnosis. Over 50% of patients had received some form of chemotherapy from general practitioners prior to admission.

In those infants under 12 months of age, an increased tension in the anterior fontanelle was the most useful sign and this was present in 64% of cases. Signs relating to meningeal irritation are generally regarded as being uncommon in childhood meningitis; neck stiffness was in fact present in 63% of patients but Kernig's sign was demonstrated in less than 20 percent. The presence of opisthotonus was of grave prognostic significance; this was noted in 4 children and indicated a fulminating or neglected infection. Focal neurological abnormalities were observed in 15% of patients at admission; the most common of these were sixth nerve palsy and hemiparesis. Papilloedema was observed in only two patients, one with a ruptured cerebral abscess consequent on a cyanotic congenital heart defect; in the other, meningitis was complicated by a massive subdural effusion.

A surprisingly high proportion (61%) of patients had significant anaemia (haemoglobin <10 gm per 100 ml) at admission. Leukocytosis (cell count $>12{,}000$ per μ) with predominance of neutrophils was encountered in 39 patients (66.1%). There was no correlation between these haematological findings and the duration of symptoms before diagnosis, nor did they reflect the severity or influence the outcome of the illness.

CSF Findings

The CSF was either turbid or frankly purulent in the majority of cases. Protein levels were elevated beyond 50 mg per 100 ml in all patients and the glucose values were lower than 50 mg per 100 ml in 51 cases. A centrifuged specimen of the CSF was subjected to Gram-stain in all cases and this demonstrated micro-organisms in 53 cases. Cultures of the CSF revealed bacteriological growth in 52 patients. In addition, blood cultures were positive in 36 out of 53 patients in whom they were performed. In two infants, *Haemophilus influenzae* was isolated from the blood whereas the CSF was sterile. Prior antibiotic administration reduced the likelihood of isolating the causative organisms. All 7 patients with sterile CSF and blood at admission had received antibiotics but in 25 patients cultures of the CSF were positive despite previous chemotherapy.

Table II

Causative Organisms in 59 Children with Purulent Meningitis. The causative agents in 25 patients with neonatal meningitis diagnosed during 1972–1977 are included for comparison.

Organisms	Childhood meningitis 1 month–12 years	Neonatal meningitis 0–1 month
H. influenzae	26	0
Strep. pneumoniae	18	0
Staph. aureus	2**	1
Staph. albus	2*	0
Flavobacterium meningosepticum	0	13
Esch. coli	1*	5
Proteus mirabilis	0	2
Klebsiella sp.	1***	2
S. paratyphi	1	0
Strep. faecalis	1	1
No growth	7	1
Total	59	25

* meningitis due to colonised ventriculo-atrial shunts.
** meningitis due to ruptured cerebral abscess and infected dermal dural sinus, respectively.
*** meningitis due to infected indwelling intravenous catheter.

The most common organisms isolated were *H. influenzae* and *Strep. pneumoniae* (Table II). All cultures of pneumococci were highly sensitive to penicillin as determined by disc agar diffusion method; isolates of *H. influenzae* (type b in 24 of 26 isolates) were all susceptible to ampicillin, chloramphenicol and trimethoprim-sulphamethoxazole. Meningitis due to other bacteria should alert to the possibility of a distant focus of infection. Retrograde spread of infection from colonised ventriculo-atrial

shunts was responsible for ventriculitis in 3 children with hydrocephalus. In one child, the infection extended from a septic focus arising in a congenital lumbar dermal dural sinus, and in another meningitis resulted from a ruptured cerebral abscess. An infected indwelling intravenous catheter was the source of infection in an infant with a congenital heart defect.

In approximately two-thirds of the cases treated, repeat examinations of the CSF were performed. Cultures were invariably negative within 72 hours of institution of appropriate chemotherapy but CSF pleocytosis, increased protein values and diminished sugar concentrations persisted for 1 to 7 weeks after bacteriological cure. The decision to suspend antibiotic treatment was based on bacteriological and clinical recovery; mild abnormalities of the CSF cytology and chemistry were not regarded as indications for continuation of chemotherapy.

Treatment

Once a diagnosis of meningitis was confirmed by lumbar puncture, parenteral chemotherapy was initiated. Chemotherapeutic regimes were variable but usually included a penicillin (Penicillin G, ampicillin or cloxacillin) in association with chloramphenicol or gentamicin. In about one-third of the patients, additional antibiotic support was provided via the lumbar thecal or intraventricular route. Chemotherapy was adjusted once culture and sensitivity results were known. Every effort was made to reduce high fever by antipyretics, exposure, sponging and occasionally by parenteral chlorpromazine. Implanted catheters were removed when these were suspected to be septic foci and pockets of infection received appropriate surgical treatment. Oral or nasogastric feeding was initiated as soon as this could be tolerated. Clinical response as judged by defervescence, increased alertness and improved appetite was usually evident within 48 hours unless complications or death occurred.

Complications

Convulsions occurred so frequently that they may be regarded as an integral part of the disease. The most common seizure pattern observed was the generalised tonic or clonic fit of short duration and low frequency. These fits were readily controlled by intermittent intravenous diazepam (valium: 0.1 – 0.3 mg/kg) or intramuscular paraldehyde (0.3 ml/kg). Less frequently, focal or generalised seizures of a recurrent and prolonged nature were encountered. In addition to diazepam, diphenylhydantoin 6–8 mg/kg per day or phenobarbitone 5–8 mg/kg/day was prescribed for these very ill patients but the fits were frequently resistant to anticonvulsive therapy. In these children, the underlying aetiology was frequently multiple and included uncontrolled infection, cortical venous thrombophlebitis and arteritis (Fig. 1), cerebral oedema and subdural effusion. This situation usually demanded a repeat lumbar or ventricular puncture to evaluate the bacteriological response to chemotherapy and bilateral subdural taps to exclude the presence of effusion.

Figure 1: Post-mortem specimen of the brain of a child with purulent meningitis. Note extensive infarct of the left hemisphere from arteritis and thrombophlebitis of the cortical vessels.

Cerebral oedema is present in almost every case of meningitis and is believed to be at least partially responsible for the increase in intracranial pressure, disturbance of consciousness and convulsions. Provided adequate antibiotics are administered, mild degrees of brain oedema should subside within

48 hours. In severe brain swelling, the immediate hazard is that of tentorial herniation with brain stem compression and death. In 15 patients, the clinical manifestations of cerebral oedema, viz. incessant convulsions, hyperpyrexia, tense fontanelle, high pitch cry, irregular respirations, unequal pupillary size, opisthotonus and deepening coma were severe enough to warrant treatment with intravenous mannitol (1–2 gm/kg over 10–15 minutes) and/or dexamethasone (1–2 mg intravenously 6 hourly). Water retention, consequent on an inappropriate secretion of anti-diuretic hormone, undoubtedly contributed to the cerebral oedema in at least 5 patients. This condition was diagnosed if the child voided a hyperosmolar urine in the presence of hypotonic extracellular fluid. Treatment was by fluid restriction until the serum sodium concentration returned to normal. Cerebral oedema was considered a major contributory cause of death in at least five of the nine patients who succumbed to the infection.

Subdural effusion was suspected in any child with persistent fever, lethargy, irritability or recurrent convulsions; with focal neurological signs; or with a bulging fontanelle or an increasing head circumference. Transillumination of the skull as a diagnostic tool was not found to be useful. In the presence of the above manifestation, diagnostic taps were performed over both parasaggital subdural spaces. Significant amounts of subdural fluid (1–50 ml) were found in 25 patients and the effusion was bilateral in 16 cases. The subdural fluid was characteristically xanthochromic with a protein level in excess of 500 mg per 100 ml. In an unexpectedly high proportion of cases (35%), the fluid revealed organisms on culture. Conservative tapping of the subdural space with a 21 gauge needle whenever symptoms recurred, was successful in controlling the effusion in all but two patients. The number of subdural taps required ranged from 1 to 12. In the 2 infants where conservative treatment failed, surgical removal of the subdural membranes was performed in one and a subdural-peritoneal shunt was inserted in the other.

In young children, bacterial meningitis is frequently part of a systemic infection. Bronchopneumonia was the most frequent associated illness noted and occurred in 10 patients. In 2 patients with *H. influenzae* meningitis, septic arthritis involving the hip and the knee joint respectively, was responsible for the persistent fever. One desperately ill infant also with *H. influenzae* infection developed a concomitant purulent pericarditis and improved dramatically after pericardial drainage.

Outcome

Fifty children survived the infection. One child with *Salmonella* meningitis relapsed one week after suspension of antibiotics but responded to a second course. The overall mortality rate was 15 percent. Mortality was much higher with pneumococcal meningitis (33%) as compared to that due to *H. influenzae* (4.5%). Six of the total deaths occurred within 48 hours of admission. Septic shock, a gross disturbance of sensorium, opisthotonus and uncontrollable convulsions were pointers to a poor prognosis. It was not possible to reach conclusions regarding the efficacy of any particular antibiotic as many different regimens were employed in treatment. Forty-seven of the 50 survivors had at least one follow-up examination after discharge from hospital. In the neurological evaluation particular attention was paid to the detection of gross auditory and visual impairment, head circumference, intellectual and developmental retardation, behaviour problems, focal neurological defects and the occurrence of seizures. The results of the examinations revealed that 30 patients were within normal expectations or were left with no detectable residual damage. There were 8 subjects with significant neurological findings which included spastic hemiparesis, spastic quadriplegia, poor vision, partial hearing loss, hyperkinetic behaviour and epilepsy. Nine patients were left with severe brain damage and were incapable of an independent existence. The age of onset, interval between onset and therapy, previous administration of antibiotics and CSF cell count did not seem to influence mortality or morbidity.

Discussion

Bacterial meningitis is a medical emergency and although this disease is well known, it still poses a formidable diagnostic challenge. When the presenting features are with convulsions, opisthotonus and coma, the diagnosis is easy but therapeutic response is likely to be disappointing. In the early stages of infection symptoms are likely to be vague and non-specific and clinical signs may be equally subtle. A high index of suspicion is important; the presence of fever, lassitude, drowsiness and irritability in a young child should bring to mind the possible diagnosis of meningitis. Empirical antibiotic therapy should be avoided and there should be no hesitation in performing a lumbar puncture if the diagnosis is in any doubt. At the University Hospital, approximately 3.5% of 1,850 lumbar punctures performed in children during a 4-year period allowed a diagnosis of bacterial meningitis and we would consider this an acceptable risk-benefit ratio.

A prompt and careful examination of the CSF will in the vast majority of cases yield a definitive diagnosis. While an increased CSF cell count with predominant polymorphonuclear leukocytosis, a

diminished glucose concentration and an elevated protein level offer corroborative evidence (Menkes, 1969), the diagnosis is confirmed by the demonstration of micro-organisms on a stained film and on culture. Blood culture will often provide additional confirmation and is occasionally positive when the CSF is sterile. The typical CSF findings may be obscured and the chances of obtaining positive cultures prejudiced by previous antibiotic therapy. Thus, when organisms cannot be demonstrated in the CSF the physician is confronted with the problem of distinguishing aseptic viral meningitis from partially treated bacterial meningitis. The problem may partly be resolved by performing a repeat lumbar puncture a few hours later while antibiotics are withheld (Smith, 1973). The recent introduction of immuno-electrophoresis to detect bacterial antigens (Edwards *et al.,* 1972) and of limulus lysate to detect endotoxin in the CSF (Nachum *et al.,* 1973) has helped overcome some of the problems. Whenever doubt exists, the safest course is to institute parenteral antibiotics at full dosages for 10 days. In this series, positive cultures were obtained from the CSF in 83% of patients. The predominant organisms, *H. influenzae* and *Strep. pneumoniae* were responsible for 85% of all cases where bacteria could be isolated. The conspicuous absence of *Neisseria meningitidis* as a causative agent is at variance with reports from Western countries. Surveys of oropharyngeal flora in the local population also confirm the rarity of this micro-organism as a commensal. Beyond the neonatal period. Gram-negative enteric organisms are rarely implicated in the aetiology. When these and other unusual bacteria are isolated from the CSF in an older child, a careful search should be made for anatomical defects in the central nervous system, for distant foci of infection, and for impaired immunity in the host.

The choice of chemotherapeutic agents for initial treatment is still controversial. In many institutions, intravenous ampicillin has been advocated. Because ampicillin achieves a CSF concentration which is 5–30% of the simultaneous blood concentration, depending on the degree of meningeal inflammation, and because of the gradual development of anti-microbial resistance, the current recommendation is to administer ampicillin at a dose of 400 mg/kg/day for 10–14 days (Haltalin and Smith, 1971). The practice of reducing the dosage after a few days is irrational. Even with this regime treatment, failures have been described and these have subsequently responded to chloramphenicol (Shakelford *et al.,* 1972). The other favoured combination is penicillin (benzylpenicillin 1 mega unit, 4–6 hourly, I.V.) with chloramphenicol (100 mg/kg/day) for 10–14 days. Both these drugs penetrate the blood – CSF barrier in sufficient quantities to attain a satisfactory CSF concentration, regardless of the degree of meningeal inflammation (Roy *et al.,* 1952). The risk of haematological toxicity accompanying the use of chloramphenicol has reduced its popularity but this must be very small compared to the seriousness of meningeal infection. Other centres have reported success with the use of trimethoprim-sulphamethoxazole combination (Roy, 1971). The role of intrathecal and intraventricular administration of antibiotics to provide additional therapeutic support is still uncertain. While intraventricular therapy has significantly reduced the mortality in gram-negative neonatal meningitis (Lee *et al.,* 1977), further evaluation is necessary before its routine administration can be recommended in the older child. The duration of antibiotic therapy depends on the clinical response. In our experience, it is safe to suspend chemotherapy once the patient has remained a febrile for 7 days. As CSF abnormalities may persist for 3 or more weeks after bacteriological cure, it is unnecessary to continue chemotherapy until the CSF returns to normal.

Supportive measures are about as important as appropriate antibiotic therapy and must not be neglected. The goal is to maintain the child's homoeostasis by providing adequate oxygenation, correcting metabolic derangements (acidosis, hypoglycaemia, hypo- or hyper-osmolarity) and ensuring a satisfactory cerebral blood flow. Maintenance of these physiological parameters will require accurate monitoring of blood pressure, fluid balance, haematocrit, and frequent determinations of blood sugar, electrolytes, PO_2 and acid-base status. Hyperpyrexia and prolong seizures will further compromise the oxygen demands of the brain and must be promptly brought under control. Subdural effusion cerebral oedema and other complications should be identified early and treated appropriately.

The mortality rates in this series are comparable to those described in the West; 4.7–19% for *H. influenzae,* and 25–37% for *Strep. pneumoniae* (Fraser *et al.,* 1973; Weiss *et al.,* 1967). Murray *et al.* (1972) was able to reduce the overall case fatality to 2.9% and attributed this improved result to the intensive supportive therapy their patients received. The incidence of long-term sequalae of this disease is distressingly high. Only about half of our patients with left with no apparent neurological deficit. Detailed psychometric and audiometric evaluations were not performed on these children, so that the incidence of more subtle brain damage is probably higher. Sell *et al.* (1972) reported that 43% of their patients with *H. influenzae* meningitis were free from detectable defects. When more extensive psychological testing was subsequently performed

on these post-meningitis 'normal' children, it was found that they were functioning at considerably lower levels than their peers (Sell *et al.*, 1972). A more aggressive approach to diagnosis and therapy will clearly be required if the mortality and morbidity risks are to be reduced.

Summary

This is a review of 59 cases of purulent meningitis in children between the age of 1 month and 12 years. The clinical features at presentation are often non-specific and diagnosis frequently masked by previous antibiotic administration. *H. influenziae* and *Strep. pneumoniae* are the two most common causative organisms. The overall mortality rate of 15% is similar to most published figures. However, only 50% of children escaped demonstrable brain damage. Currently, penicillin with chloramphenicol or ampicillin alone are recommended for initial therapy. If results are to be significantly improved, the infection must be detected in its early stages by the liberal use of lumbar puncture while antibiotics are withheld. The goal in chemotherapy is to ensure an adequate concentration of the appropriate antibiotic in the CSF. In addition, treatment must be directed towards the prevention and prompt management of the metabolic derangement and other complications accompanying the disease.

Acknowledgements

We are grateful to Professor M.J. Robinson and Associate Professor K.H. Chai for permission to study the clinical and laboratory records, and to Dr. R.O. Johnson for his helpful criticisms in the preparation of the manuscript. Mrs. Ng Mo Tsing provided the secretarial assistance.

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