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NON-MENINGOCOCCAL PURULENT MENINGITIS IN INFANCY AND CHILDHOOD

A STUDY OF 52 CASES *

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The diagnosis of meningitis until relatively recently carried with it an extremely gloomy prognosis, causing despair to both the parents and the paediatrician. The introduction of the sulphonamides and antibiotics has completely changed the outlook for patients suffering from purulent meningitis. It has been stated that the mortality rate should not exceed 10% in cases of meningococcal and 'influenzal' meningitis and 20% in pneumococcal meningitis.¹

This paper deals with a study of 52 cases of purulent meningitis in infancy and childhood treated at Groote Schuur Hospital in the 2 years July 1955 to June 1957. The series comprises 22 cases caused by the pneumococcus, 9 by *Haemophilus influenzae* and 10 by *Haemophilus para-influenzae*, and 11 cases where a causal organism was not identified with certainty (of which the cerebrospinal fluid (C.S.F.) obtained on admission was purulent in every case and in 6 cases showed organisms in stained preparations, but in no case was the organism isolated on culture). Meningococcal infections are not treated at Groote Schuur Hospital but at the City Hospital for Infectious Diseases, Cape Town, and thus do not appear in the series. A few rare forms of meningitis seen during this period are excluded.

Of the 52 patients 36 were aged 7 months and less, 11 were between 7 months and 1 year, and 5 were older than a year. Only 3 were Europeans. A large number were malnourished, many had rickets and most had some degree of anaemia. Several had severe diarrhoea complicating their illness and required parenteral administration of fluid.

The objects of the study were:

1. To test a simple therapeutic regime for pyogenic meningitis.
2. To determine the speed with which the CSF becomes sterile.
3. To correlate the timing of CSF changes with immediate prognosis during treatment.

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4. To estimate the significance of continued pyrexia.
5. To assess the prognostic significance of the clinical picture on admission.

SCHEME OF TREATMENT

In 22 cases the patients received no intrathecal treatment. Because of the delay in arranging for admission to our overcrowded wards, all the other children were given an intrathecal injection immediately after the withdrawal of CSF for diagnostic purposes—15 cases received 10,000 units of penicillin, 12 cases 200 micrograms of chloramphenicol, and 2 cases 10,000 units of penicillin plus 200 micrograms of chloramphenicol. Further treatment was determined by the apparent aetiology as judged by the smear made from the first specimen of CSF. When the result of the culture became available the treatment was modified or altered if the initial assessment was shown to be at fault.

Pneumococcal Meningitis. Tetracycline has a wide range of anti-bacterial activity and is known to cross the blood-brain barrier well.²⁻⁵ It was decided to treat our cases of pneumococcal meningitis with this antibiotic. After a loading dose of tetracycline hydrochloride (Achromycin, Lederle), 10 mg./lb. by intramuscular injection, it was continued in a dosage of 10 mg./lb./day divided into 3 eight-hourly intramuscular injections. Sulphadiazine was given in addition, 2 gr./lb./day orally, or by stomach tube in comatose patients. In 6 cases, only tetracycline was given.

Haemophilus influenzae and para-influenzae. In the influenza cases, after a loading dose of chloramphenicol, 50 mg./lb. by intramuscular injection, treatment consisted of chloramphenicol 50 mg./lb./day in 8-hourly doses by intramuscular injection. Oral sulphadiazine was also given, as in the pneumococcal cases.

Cases where No Organism was Identified. Of these cases, 7 received chloramphenicol, tetracycline and sulphadiazine, 2 received tetracycline and sulphadiazine, 1 received chloramphenicol and sulphadiazine, and 1 received tetracycline only.

This variation in treatment was due to the uncertainty of the aetiology and occasionally to misinterpretation of instructions. Treatment was often decided by a knowledge of which drugs the patient had received before admission. Some patients were doing so well on the provisional treatment started before receipt of the culture report that it was not changed, even though the suspected type of infection was not confirmed.

Treatment was continued for 10 days in all the groups. Sedatives were used liberally. As the condition of the patients improved the drugs were given orally.

RESULTS OF TREATMENT

Table I shows the results of treatment. There were 22 cases of pneumococcal meningitis with 16 recoveries, i.e. a recovery rate of 73%. Of the 6 children who received tetracycline but no sulphadiazine, 4 recovered. There were 19 cases of haemophilus meningitis with 14 recoveries, i.e. a recovery rate of 74%. In the non-identified group 10

TABLE I. RESULTS OF TREATMENT

	Cases	Recoveries	%	Deaths
Pneumococcus ..	22	16	73	6
H. influenzae ..	9	7	74	2
H. para-influenzae ..	10	7		3
Not identified ..	11	10	91	1
	<u>52</u>	<u>40</u>	<u>77</u>	<u>12 (23%)</u>

survived out of 11 cases seen, i.e. a recovery rate of 91%. The child who died had received a combination of all three drugs. In the last-mentioned group more than half had had some form of treatment prescribed before admission to hospital and it is possible that some of these infections were already partially controlled by this treatment.

It is generally accepted that meningitis carries a graver prognosis in the early months of life than in later childhood. Most of our cases were 7 months old and younger; 36 fell into this group (about 70%); 11 were between 7 months and 1 year; 5 were over one year of age, the oldest being 5 years.

The results of treatment in the age-group 7 months and under are shown in Table II. There were 16 pneumococcal

TABLE II. RESULTS OF TREATMENT IN THE AGE-GROUP 7 MONTHS AND UNDER

	Cases	Recoveries	Deaths
Pneumococcus ..	16	10	6
H. influenzae ..	5	4	1
H. para-influenzae ..	8	5	3
Not identified ..	7	7	—
	<u>36</u>	<u>26</u>	<u>10</u>

cases with 6 deaths. There were 5 influenzal cases with 1 death, and 8 para-influenzal cases with 3 deaths. No deaths occurred in the 7 children of the unidentified infections. Thus, out of a total of 12 deaths in the whole series, 10 occurred in this age-group; that is to say, 83% of the deaths occurred in babies less than 8 months old.

Time of Death. Of the 'pneumococcal' deaths 3 occurred within 24 hours of admission, one of them within the first hour; 2 died on the 6th day and 1 on the 16th. Of the 'haemophilus' deaths 2 occurred on the 3rd day, 1 on the 7th, 1 on the 17th and 1 on the 28th. The child in the non-identified group died on the 10th day.

Autopsies were performed in 7 cases. The residual menin-

geal exudate was cultured in 2 cases, but the causal organism could no longer be isolated. In one case death appeared to be due to a terminal staphylococcal septicaemia. One patient was found to have a cerebral abscess in addition to meningitis. Subdural effusions were not found.

Neurological Sequelae. These are shown in Table III. Among the pneumococcal cases there were 2 mentally retarded and spastic children. One was a baby of 2 months, and the other was a child of 14 months who had been retarded and epileptic before his illness. A 7-month-old

TABLE III. RESULTS IN 39 SURVIVORS

	Pneumo-coccus	Haemo-philus	Not identified
Mentally retarded and spastic ..	2	—	1
Spastic hemiparesis or hemiplegia ..	1	1	—
	<u>3</u>	<u>1</u>	<u>1</u>

infant had a spastic hemiparesis which was rapidly improving when seen as an out-patient two weeks after discharge. Among the haemophilus group one 10-month-old infant was left with a spastic hemiplegia. Among the non-identified group an 11-month-old was left spastic and retarded.

CLINICAL PATHOLOGY

Bacteriology of the Cerebrospinal Fluid

Preparations of the initial specimens of CSF were stained with Gram's stain. The causal organism was found in all the cases of pneumococcal and *H. influenzae* infection and confirmed by culture. In the 10 *H. para-influenzae* group the organism was found in 7 of the initial smears; in 2 no organism was seen and in 1 the appearance of the organism was equivocal. Culture of these 10, however, demonstrated the nature of the infection.

In the group where no organism was isolated on culture, Gram-negative bacilli had been seen on the initial smear in 2 cases and Gram-positive diplococci in 4.

Table IV shows the results of CSF culture after 48 hours' treatment. In the pneumococcal group 11 of the 12 fluids

TABLE IV. CSF CULTURE AFTER 48 HOURS' TREATMENT (32 CASES)

	Negative	Positive
Pneumococcal ..	11 } 14	1
H. influenzae ..	*3 } 26	3
H. para-influenzae ..	4 } 12	6
	6 } 8	2
	*2	

* After 24 hours' treatment.

were sterile. The 3 most recent cases were checked at 24 hours and found to be sterile. The *H. influenzae* group showed 4 sterile out of the 7 cultured at 48 hours, and in the *H. para-influenzae* cases 6 of the 8 tested were sterile. Again, the CSF of the 2 most recent cases of para-influenzae infection was cultured at 24 hours and showed no growth.

Of the 6 children who had positive CSF cultures 48 hours after the commencement of treatment 3 died and 1 had a residual hemiplegia. Of the 14 patients in the pneumococcal group with sterile fluids at 48 hours, 2 died and 2 are mentally retarded. The 4 in the influenzal group all recovered completely but in the para-influenzal group, of 8 children with sterile 48 hour cultures, 2 died. Thus, though treatment produced rapid sterilization of the CSF, there was a cont

siderable mortality and morbidity. There was no recurrence of infection in any case of the series.

Other Changes in the CSF. In all but one of the 52 patients there was initially a polymorph preponderance on the CSF smear. The exception was a case of *H. para-influenzae* meningitis which showed a mononuclear picture. Pandy's

TABLE V. QUALITATIVE SUGAR ESTIMATION

	Cases	Absent	Diminished	Normal
Pneumococcus ..	12	7	3	2
H. influenzae ..	8	6	2	0
H. para-influenzae ..	9	4	4	1
Not identified ..	9	5	3	1
	38	22	12	4

test for increased globulin was positive in 38 cases out of 39 tested. It was negative in 1 case of pneumococcal meningitis. The sugar content of the CSF showed considerable variation on qualitative testing (Table V). In 38 cases, sugar was absent in 22, diminished in 12 and normal in 4.

At the commencement of the study we were uncertain whether treatment should be continued until the CSF was completely normal. In 3 cases abnormalities persisted into the 3rd week and in 2 others beyond the 4th week. These 5 children all became normal despite the fact that treatment had not been prolonged beyond the standard time. In these cases, however, the cells persisting in the CSF were mononuclears and the sugar had returned to normal or nearly so. It appears that if the CSF is sterile a raised cell count does not necessitate prolongation of therapy so long as the sugar is returning to normal and the cellular response is not polymorphonuclear.

PROGNOSIS

The Significance of Continued Pyrexia

In most cases the temperature settled after the 4th day of treatment, but in a fair number it persisted for a week. Subdural taps were done on 11 of these children and were found to be positive in 5. Where subdural effusions were present, there were other signs in addition to pyrexia, e.g. continuing convulsions, increasing spasticity, deepening coma, and full fontanelle. It would appear that when persistent pyrexia is the only untoward sign the prognosis is not likely to be adversely affected.

The Prognostic Significance of the Clinical Picture on Admission

Table VI shows the course taken by the cases in relation to their state on admission.

Ten children were comatose on admission. Of these 7 died, 2 recovered completely and 1 who had been retarded before his attack of meningitis remained so. Four of these comatose children were spastic and, of these, 3 died and the other was the retarded child. One comatose child had one spastic limb and recovered completely. Among the 5 comatose children who showed no evidence of spasticity 4 died and 1 recovered completely. Thus 70% of the children comatose on admission died.

Twelve children were stuporose on admission. Of these, 3 died, and of those who recovered 1 was retarded, 1 had a hemiplegia and 1 a hemiparesis, and 6 recovered completely. Three of these stuporose children were spastic and, of the three, 1 died and 1 was hemiplegic and 1 hemiparetic. Two of the stuporose children had spasticity in a single limb and

TABLE VI. ADMISSION STATE AND PROGNOSIS

	Cases	Deaths	Sequelae	Normal	
Coma					
+ generalized spasticity ..	4	3	1	—	
+ localized spasticity without spasticity ..	5	4	—	1	
Total ..	10	7	1	2	
Stupor					
+ generalized spasticity ..	3	1	2	—	25%*
+ localized spasticity without spasticity ..	7	1	1	5	
Total ..	12	3	3	6	
Conscious					
+ spasticity (hemiplegia) ..	2	1	1	—	7%
without spasticity ..	28	1	—	27	
Total ..	30	2	1	27	

* Mortality.

of these 1 died and 1 is normal. Of the 7 stuporose children without signs of spasticity 1 died, 5 are normal and 1 was left with a hemiparesis. Thus 25% of the children stuporose on admission died.

Thirty children were conscious on admission. Of these 2 died. Two of the conscious children had a spastic hemiplegia on admission. One died and autopsy revealed a cerebral abscess. The other was left spastic and retarded. Thus 7% of the children conscious on admission died.

These findings suggest that coma is a grave prognostic sign. Stupor and spasticity also adversely affect the outcome. No child showing generalized spasticity on admission recovered completely.

Chest Radiography

Radiographs of the chest were taken in 48 cases. The results are shown in Table VII. In 20 cases of pneumococcal meningitis bronchopneumonia was found to be present in 7, lobar pneumonia in 1, and pulmonary tuberculosis in 1. In 15 cases of haemophilus infection 3 children showed

TABLE VII. RESULTS OF X-RAY EXAMINATION OF THE CHEST

	Cases	Broncho-pneumonia	Lobar pneumonia	Tuber-culosis	Empyema
Pneumococcus	20	7	1	1	—
Haemophilus	17	3	—	—	1
Unidentified	11	3	—	—	—
	48	13	1	1	1

bronchopneumonia and 1 empyema. Three cases of bronchopneumonia were found in the 13 belonging to the unidentified group. Thus pneumonia occurred most frequently in the cases of pneumococcal meningitis, but no correlation could be found between this finding and the course or result of the meningitis.

COMMENT

While this series is not large enough to permit of many definite conclusions several interesting facts emerge.

Out of the 22 cases of pneumococcal meningitis 16 sur-

vived. If the cases dying within 24 hours of admission are excluded, there were 16 survivals out of 19 cases, a recovery rate of 83%. We may conclude that tetracycline plus sulphadiazine is an effective combination. The fact that there were 4 survivors out of the 6 cases treated with tetracycline only, further suggests that tetracycline is an effective drug for the treatment of pneumococcal meningitis.

Out of the 19 cases of haemophilus infection 14 survived. It is surprising that this group did not do better than the pneumococcal group. It may be that the onset of haemophilus meningitis is more insidious and that our patients did not come to hospital until the disease was well advanced.

Out of the 11 in the unidentified group 10 survived. This suggests that this group carries a very good prognosis; but it is difficult to deduce which is the best drug or combination of drugs to use in treating them.

The results are encouraging which were obtained with this simple regime of one intrathecal injection at the time of the discovery of a purulent CSF and systemic treatment only thereafter. The virtual exclusion of intrathecal treatment makes it a method of treatment applicable to country practice. An over-all recovery rate of 77% in cases of purulent meningitides, in patients of non-European race and with indefinite but frequently prolonged illness before the institution of treatment, may not be the best obtainable, but under such circumstances and in such subjects is at least an improvement on former results.

In 26 of the 32 CSF cultures checked 24-48 hours after the start of treatment, there was no growth. Of the 7 deaths in these 32 children, 4 were in those with negative 48-hour cultures, and such negative culture is therefore not a reliable prognostic point. The fact that in the 39 survivors there were no relapses of the infection indicates the adequacy of the anti-infective therapy.

Coma is the gravest single prognostic sign. The occurrence of spasticity also adversely affects the prognosis. More intensive treatment or some adjuvant to the current

anti-infective treatment may be required. The use of cortisone merits consideration and closer attention to electrolyte disturbance and its importance in the production of cerebral oedema may be beneficial. The finding of 5 survivors with serious sequelae, though this is not a high figure—13% of the survivors—seems to point in the same direction, namely, concentration on the non-bacterial aspect of meningitis.

SUMMARY

1. A simple scheme for the treatment of pyogenic meningitis is described. This consists of an initial intrathecal injection followed by systemic treatment only.
2. The results of this regime in 52 cases are described. The general recovery rate was 77%.
3. Effective sterilization of the CSF was shown in 26 of 32 tests made within 48 hours of starting treatment.
4. Persistence of some fever for a week, or of a raised CSF cell count for as long as 4 weeks, was not of bad prognostic significance.
5. Of the 39 recoveries 5 were associated with serious sequelae.
6. Coma at the time of admission was associated with a 70% mortality and stupor with a 25% mortality.
7. No patient showing generalized spasticity on admission recovered completely.
8. It is suggested that further improvement in mortality figures will be dependent on measures other than the anti-bacterial treatment.

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