A FOLLOW-UP STUDY OF 110 PATIENTS TREATED FOR PURULENT MENINGITIS

BY

ELLY M. DESMIT

From the Juliana Kinderziekenhuis, The Hague

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As modern therapy has undoubtedly changed the course and prognosis of purulent meningitis, this study was undertaken in order to review the course of our cases and to gain an impression of the ultimate results. For the immediate result all the notes on patients treated in the period from October, 1949, to March, 1954, were scrutinized. In addition, all the patients of this period who survived were checked regarding their physical and mental development at least six months after discharge from hospital. The children were tested according to the directions of Gesell and Amatruda outlined in their book on developmental diagnosis and by the method of Binet-Simon. In addition the behaviour of the child in his surroundings was taken into account, and his development before his illness. For example, when a mongolian idiot developed in a similar fashion after meningitis as before his illness, he was marked as undisturbed.

In the period concerned 114 patients with purulent meningitis were admitted to the Juliana Kinderziekenhuis. Of these patients the aetiological diagnosis was made by direct examination and culture of the cerebrospinal fluid.

When an operation was performed on the mastoids a culture of the pus was made as well. In cases showing the syndrome of Waterhouse-Friedrichsen a direct smear was made from the petechiae. By these methods a definitive bacteriological agent was found in 99 cases; in the remaining 15 patients the aetiology was not clear.

Apart from the cases of influenzal meningitis the treatment was much the same in all cases: penicillin, 3-hourly 20-50,000 units, and sulphadiazine, daily 100-200 mg./kg. body weight. In addition, 10,000 units of penicillin diluted in 10 ml. saline were given in some cases intrathecally, mainly at the end of the diagnostic puncture and sometimes for the first few days afterwards as well. In the cases of *H. influenzae* meningitis, the therapeutic scheme divides into two periods. In the first period, until 1951, patients were treated with penicillin three-hourly 20-50,000 units, streptomycin 40 mg./kg.

body weight, and sulphadiazine 100-200 mg./kg. In addition, a number of these patients had one or more intrathecal injections of penicillin and/or streptomycin, 1/10-1/15 of the daily dosage. Then chloramphenicol became available, and patients admitted in 1951 and later were treated with a combination of chloramphenicol, 125 mg./kg., and sulphadiazine, 100-200 mg./kg., as soon as they had stopped vomiting.

Of the total of 114 patients, 10 died, including two deaths in children after they had recovered from meningitis. One of these children died from a haemorrhagic diathesis for which he had been admitted on several other occasions. The other child, suffering from a transposition of the great vessels, died six months after meningitis. As it was not possible to give a definite judgment on possible late effects of the meningitis, these patients are not recorded. For the same reason two out of 104 surviving patients are not included in this survey as they did not appear for our routine examination.

Although our results do not look bad at first sight, as only eight patients out of 110 died, the final results are depressing. Of the 102 surviving patients, 16 presented defects, more or less interfering with normal life and development.

When comparing the notes of the patients who still suffer from the sequelae of the 'cured' meningitis, attention is drawn to a certain similarity in the condition of some of them during the acute illness. They were ill several days before admission. On admission symptoms of a focal brain process were manifest. They had convulsions in one arm or one leg or one side of the face. Often they turned head and eyes to one side. They often remained comatose for some days. They had a strange, wild gaze. If there had not been neck rigidity, and sometimes a bulging fontanelle, undoubtedly the diagnosis would have been stated as encephalitis. The following case is an instance.

Case 94. A baby of 7 months, who had had a cold 14 days previously, became ill again one day before

admission. He was drowsy, refused food and then had a convulsion, with contractions in the left arm. On admission he was comatose and had a convulsion involving the right arm and right side of the face. The following two days the condition remained unchanged. The right arm was stretched spastically with the fingers clenched round the thumb and occasionally contracted. In the next few days the condition seemed to improve. The child took his feeds, had no convulsions, the cerebrospinal fluid cleared and the temperature became normal. As the right arm and leg still remained spastic the child was referred to a neurosurgical clinic (the Ursulakliniek) where the E.E.G. showed disturbances on the left side, parieto-occipito-temporal. Trepanation was performed, but there was no hygroma.

In the follow-up study the child appeared to be mentally retarded (I.Q. 60), he had a paresis of the right arm and leg, and was suffering from salaam convulsions.

Case 108. A baby of 7 months, who had been ill for eight days before admission, had had convulsions on the first day. He was rigid, had a squint and, notwithstanding therapy, convulsions started again after two days. The left arm and leg were spastic and the head and eyes continually turned to the left. An operation on the mastoids did not give any improvement. His left arm and leg were moving continuously, and the right arm and leg seemed to be paralytic and showed higher reflexes. Although the cerebrospinal fluid cleared, this child too was transferred to the Ursulakliniek in order to exclude an abscess or hygroma. No fluid was found. The E.E.G. showed an independence in activity of the left and right hemispheres probably caused by a derangement of the brain-stem. Encephalography showed abnormal dilated ventricles, especially on the left side. The end-result is rather tragic: the child is a hopeless mental defective with an I.Q. of 30; convulsions are controlled by 'luminal' and diphantoin, but now and again an akinetic equivalent interrupts his activities. The right arm is spastic.

Both these children were suffering from *H. influenzae* meningitis, both had penicillin, streptomycin and sulphadiazine initially, followed by a course of chloramphenicol and sulphadiazine after two days. The first child (No. 94) had an initial injection of penicillin intrathecally, the other had no penicillin intrathecally. In both cases the results are equally poor and probably due to a meningoencephalitis.

In our series of *H. influenzae* meningococcal and pneumococcal meningitis we find equivalent examples of this kind as might be shown in the survey. In one case the disturbances are severe, in another there is less interference with the mental development. And a very few cases, which showed initially severe damage and definite signs of meningoencephalitis, were found to be quite normal afterwards. For instance:

Case 109. When aged 18 months this child was admitted to the hospital for a very acute illness. He showed the syndrome of Waterhouse-Friedrichsen; he was shocked and the body was covered by petechiae. On his left cheek was a blister raised by burning, from which meningococci were cultured. With an intravenous drip of 'macrodex', noradrenalin and cortisone he recovered from the shock, but still remained unconscious, his head turned towards the right side. Three days afterwards he seemed to react a little. After some days it was obvious that he did not see; there was no reaction at all to moving subjects unless they made a noise as well. The pupils contracted normally when stimulated by light. After 23 days he recovered his perception for light and imitated the nurse when putting out her tongue. No damage could be found afterwards. Most probably the original lesion was localized in the calcarine area. Perhaps there was a little bleeding with a minimal destruction, but at the time of onset a larger area of irritation causing functional defect.

An equally surprising good result was obtained in a very bad case of pneumococcal meningitis.

When, in the following survey, the condition of the patient is stated as a remnant of meningoencephalitis, the clinical course during the acute illness has been much the same as in the above-mentioned cases.

Fig. 1 relates the distribution of the different types of meningitis to the age of the patients. As can be seen from Fig. 1, pneumococcal meningitis in particular gives rather poor results: of 24 cases, there were three of meningoencephalitis leading to a child with convulsions and I.Q. of 50%, to a child with ataxia of the right hand and I.Q. of 70%, and to a child with a spastic right leg and arm and I.Q. of 40%, respectively. In addition, another five cases were found to have the following defects: one child with a paretic right foot, one deaf and dumb child, one hydrocephalic child (she died two years after discharge from hospital), one child with aphasia and one child with an I.Q. of 70. The only child who died had been in hospital for 36 hours. On eight of these 24 patients an operation on the mastoids had been performed.

Regarding the 38 cases of meningococcal meningitis, we might conclude that here the danger is in the very acuteness of the disease, especially in the cases with the Waterhouse-Friedrichsen syndrome. Too often no proper chance is left for treatment once the patients enter hospital. The five fatal cases died three, six, eight, 12 and 24 hours after their arrival. It may be stressed here that full attention should be given to anti-shock therapy: we use an intravenous drip of 'macrodex' with cortisone and noradrenalin. Of the cases showing defects, two had had

FIG. 1.

meningo-encephalitis: one child now has convulsions and an I.Q. of 30, one child had an aphasia and partial deafness on the right and total on the left side, while of the other three children with defects, one child is suffering from an alexia, one from alexia and agraphia and one has convulsions.

Considering the cases of *H. influenzae* meningitis, we find here the two distressing cases described previously. The one fatal case expired 15 minutes after admission. In *H. influenzae* meningitis chloramphenicol combined with sulphadiazine seems to be superior to a combination of penicillin, streptomycin and sulphadiazine. Since chloramphenicol was introduced no relapses occurred, and the average time in which the C.S.F. cleared to less than 30 cells per c.mm. was remarkably shorter, 16 days; before chloramphenicol was used the average was 25 days and in addition three cases had relapsed.

In our series of sterile purulent meningitis the results have been excellent: none died and not one child shows sequelae.

There has been one case of streptococcal meningitis in a baby of 1 month who died after 10 hours, and one case of *Bact. coli* meningitis in a baby of 10 days. This child is now deaf and also suffers from a congenital dislocation of the hip.

We now wonder if we could expect an improvement in the results from a change in the therapy. Perhaps it would be advisable to give a higher dosage of penicillin, especially in the cases with meningo-encephalitis, where the outlook is worse than in meningitis. It does not need to be stressed that in any case of meningitis at least two antibacterial agents should be used in order to prevent the development of resistant strains.

There still seems to be one point of discussion regarding the use of medication intrathecally. Some authors advise against this method as they think the

intrathecal injection may be the cause of the resulting defects. In order to find out whether our cases permit us to come to a conclusion, we have divided them into two categories, with and without intrathecal therapy.

After subtracting the four cases of meningococcal and the one case of influenzal meningitis dying within 12 hours, the final results were 54 cases with intrathecal penicillin (46 good, eight damaged, no death), 51 cases without intrathecal penicillin (41 good, seven damaged, three deaths).

From these figures we cannot state that penicillin, when used intrathecally, is injurious, neither is it possible to state that it is advantageous. However, when considering again the 110 cases, no example could be found where any complications occurred directly connected with an intrathecal injection. On the other hand two cases did show a marked improvement after some days as soon as penicillin was used intrathecally. In these two cases initially no penicillin was given intrathecally. According to the investigations of Dowling, Sweet, Robinson, Zellers and Hirsch (1949) a concentration of 0.05-1.25 units of penicillin ml. was reached in the C.S.F. after only eight hours, even when penicillin was given intravenously in the extremely high dosage of 1,000,000 units two-hourly. According to Alexander, Flippin and Eisenberg (1953), the pneumococci show a delayed growth in a concentration of the penicillin of 0.03 units per ml., so one can only expect any effect from penicillin injected intravenously after eight hours. By giving the penicillin intrathecally one might be able to reduce this delay.

Although in those cases with focal symptoms we looked for a brain abscess or an accumulation of subdural fluid, we found none.

There is one point which should be stressed

TABLE

Type	Intrathecal Medication				No Intrathecal Medication		
	Death	Damaged	Improved after Intrathecal Penicillin	Good	Death	Damaged	Good
Meningococcal ..	1	1 alexia 1 meningo-encephalitis (convulsions + I.Q. 50%)		11	4	1 alexia 1 convulsions 1 meningo-encephalitis (aphasia)	17
Influenzal ..	0	1 meningo-encephalitis (No. 108) 1 partial deafness		16	1	1 meningo-encephalitis	11
Pneumococcal ..	0	2 meningo-encephalitis (1 ataxia R. hand + I.Q. 70%; 1 convulsions + I.Q. 50%) 1 hydrocephalus 1 3 attacks of meningitis since trauma skull	1 aphasia 1 paretic R. foot	5	1	1 meningo-encephalitis (spastic R. leg + arm + I.Q. 40%) 1 deaf and dumb	10
Sterile ..	0	0		12	0	0	3
Coliform ..					1	1 deaf and dumb	
Streptococcal ..							
Total ..	1	8	2	44	7	7	41

regarding the sequelae which can occur sometimes after a 'cured' meningitis. It seems to be our duty to review these children later on to see whether we still might be able to improve their condition. In some cases we might advise speech therapy, other children should be referred to a deaf and dumb asylum, and in spastic children massage can improve their condition.

Summary

A follow-up study is presented of cases treated for purulent meningitis in the period from October, 1949, to March, 1954. The suggestion is made that in some cases, where from the onset symptoms of a focal irritation of the brain were present and no abscess or accumulation of subdural fluid could be found, a meningo-encephalitis rather than a meningitis alone had led to the residual defects. The

prognosis is worse in these cases. Initial intrathecal injection of penicillin is advised, in addition to the treatment with two antibacterial agents.

In cases with *H. influenzae* a combination of chloramphenicol and sulphadiazine gave very good results. All cases of purulent meningitis should be reviewed in a follow-up study.

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