TUBERCULOUS MENINGITIS

BY

G. DONALD W. McKENDRICK, and R. J. GROSE

From the Infectious Diseases Unit, St. Ann's General Hospital, London

There are divergent views on the best method of treating tuberculous meningitis and particularly on the need or otherwise for intrathecal streptomycin (Smellie, 1954; Lorber, 1956). In a previous series one of us reported 31 survivors out of 60 cases (McKendrick, 1952). Three of these have since died, giving a survival rate of 47%. In July, 1952, isonicotinic-acid hydrazide (I.N.H.) became available and since then all cases of tuberculous meningitis have received this drug in addition to streptomycin. The results are set out below.

Present Series

Between July, 1952, and April, 1954, 58 cases of tuberculous meningitis were treated. Patients were admitted from a wide area and included some transferred from other hospitals because they were doing badly.

Criteria

Diagnosis.—Tubercle bacilli were recovered from the cerebrospinal fluid (C.S.F.) in 54 cases, organisms being seen on direct film in 50 cases in addition to being cultured. Of the four patients from whom tubercle bacilli were never recovered, one had miliary tuberculosis, one had an active primary complex, and the other two had classical histories and C.S.F. changes and were deteriorating under observation until treatment was started. Their subsequent course left no doubt about the correctness of the diagnosis.

Cure.—All 47 survivors have been under observation for at least two years since the diagnosis was made and over one year since they left hospital.

Severity.—Cases were classified on admission into one of three groups similar, but not identical, to those recommended by the Medical Research Council (1948).

Group I: Slight or no meningeal signs
Group II: Meningeal signs but no focal signs, or at most involvement of one cranial nerve. Disorientated patients were included in this group.

Group III: Either (a) in coma, or (b) with gross focal signs (e.g., hemiplegia, multiple cranial nerve palsies)

Treatment

Intramuscular and intrathecal streptomycin were given as before (McKendrick, 1952) but oral I.N.H. was substituted for para-amino-salicylic acid. All patients received I.N.H. and intramuscular streptomycin for a minimum period of six months. From August, 1953, the length of intrathecal treatment was steadily reduced, and four of the later patients had 28 intrathecal injections instead of a previous minimum of 42. The criteria for stopping intrathecal treatment remained the same as before, viz., (1) satisfactory physical and mental progress, (2) weight stationary or preferably increasing, and (3) C.S.F. showing cells and protein steadily approaching normal and a sugar above 40 mg. % (vide infra).

In addition, three patients had "viomycin", and the purified protein derivative of tuberculin was used intrathecally in three fatal cases and in two patients who recovered. All patients remained in hospital or a convalescent home for 12 months from the start of treatment.

Age

The age distribution is set out in Table I. Cases fell predominantly in the two age groups 0-4 and 15-19 years, the ages in which primary tuberculosis is known to be most serious. Of the 19 patients in the 15-19 age group, 10 were classified as being in Group III and seven of these 10 patients died. There was only one death among patients over 20 years. One man aged 67 years with a complicating miliary
tuberculosis made an uneventful recovery but was left with bilateral deafness.

**Grading**

Table II shows the mortality related to the severity on admission. The importance of early diagnosis is clearly shown, there being only one death in Grade II and none in Grade I patients. Fig. 1 confirms the finding of Taylor (1954) that the severity on admission is not related to the length of history; indeed the majority of severe cases had histories of under 10 days and only 13 patients in the whole series had been ill over two weeks. Although some Group III patients deteriorated rapidly shortly before admission most of them had had symptoms for which they might well have been referred to hospital three or more days earlier.

**Table II**

<table>
<thead>
<tr>
<th>Grade</th>
<th>No. of Cases</th>
<th>No. of Deaths</th>
<th>% Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>12</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>II</td>
<td>25</td>
<td>1</td>
<td>96</td>
</tr>
<tr>
<td>III</td>
<td>21</td>
<td>10</td>
<td>52.4</td>
</tr>
<tr>
<td>Totals</td>
<td>58</td>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>

**Cerebrospinal Fluid**

Analysis of the cerebrospinal fluids on admission showed a variation in cells from 32 to 1,250 with the majority (35 cases) between 100 and 400. Forty-two patients had protein levels between 100 and 400 mg.%. The value of a low C.S.F. sugar in diagnosis is well known. A normal sugar, however, is not rare (Flucker, 1954; McKendrick, 1954; Taylor, 1954) and seven patients in this series had levels over 50 mg. per 100 ml. on admission. In only two, however, did the level not fall below 40 mg. per 100 ml. at some time either before or during treatment.

The distribution of the C.S.F. sugar levels on admission is shown in Fig. 2. In the bulk of the cases in all groups these fell between 20 and 40 mg. per 100 ml. and it can be seen that there was no relationship between the sugar level and the grading on admission. Similarly, no correlation was found when the sugar level was related to the length of history. In common with other workers (Lorber, 1954; Ashby and Grant, 1955) we have always regarded a satisfactory C.S.F. sugar level as one of the indications of progress and intrathecal treatment has usually been continued until this is above 40 mg. per 100 ml. In seven patients intrathecal treatment was stopped with the sugar below this level and all recovered. Six of these patients had had over 90 days’ continuous intrathecal treatment, the other having had 58 injections. In five of them the sugar level reached 40 mg. per 100 ml. within four weeks, but in one it took nine weeks and the other 21 weeks after intrathecal treatment ceased. Among those who survived, the C.S.F. sugar reached 40 mg. per 100 ml. in one week in 17 patients, two weeks in eight patients, and three weeks in seven patients. The remainder took varying periods up to 34 weeks. The steady rise of C.S.F. sugar after starting treatment is a good prognostic sign, but it appears that if progress is otherwise satisfactory intrathecal streptomycin should not be continued just because of a low C.S.F. sugar level.

**Other Tuberculous Lesions**

Table III sets out the other tuberculous lesions found. The presence of miliary tuberculosis did not affect the prognosis in Groups I and II patients. The numbers are too small for firm conclusions but it is very suggestive that of seven Group III patients...
in whom no other tuberculous focus was discovered only one died whereas eight out of 13 patients in this grade with miliary disease succumbed.

**Complications**

**Cranial Nerve Palsies.**—On admission 17 patients had 27 cranial nerve palsies between them. The seventh, third, sixth, and fourth nerves were affected in that order of frequency. Fifteen palsies developed after treatment had started, the majority (12) in the first 14 days. Recovery was complete in all survivors.

**Paraplegia and Spinal Blocks.**—Evidence of a spinal cord lesion occurred in eight patients (four deaths), a similar incidence to that reported by Brooks, Fletcher, and Wilson (1954) who recorded 10 cases of transverse myelitis in a series of 80 patients. Four (three deaths) of our patients also developed a spinal block, the paraplegia appearing first in two of them at the same time as the block in one and five weeks after the block in the other. Three became frankly spastic with extensor plantar responses. Of these one died, one (a child) recovered completely after six months' gross paraplegia in flexion, and the other is left with limited spasticity. Thus of the four paraplegics who survived only one had any residual disability.

In addition to the four patients with paraplegia who developed spinal blocks, spinal block also occurred without evidence of cord damage in four other patients, two of whom died. This gives an overall mortality rate of 62% in patients who developed a spinal block.

**Intracranial Block.**—One girl developed a block in the aqueduct of Sylvius for which a Torkildsen's operation was finally done. After this she was stuporous for a month and developed bilateral third nerve palsies. She has since made a complete physical and intellectual recovery and has now been under observation for over three years.

**Blindness.**—Temporary bilateral blindness occurred in one patient. This started in the third month of treatment with loss of colour vision and progressed to complete loss of vision without retinal changes. It was thought that this might be due to I.N.H. and full recovery occurred within three months of stopping this drug. Optic neuritis due to I.N.H. has been reported (Keeping and Searle, 1955).

**Results**

There were 47 (81%) recoveries in the series of 58 patients. Serious complications among the survivors were few, and at two years from the onset of treatment there were only five patients with a disability sufficient to interfere with their leading a completely normal life. The disabilities consisted of severe deafness (two patients), paraplegia (one patient), hemiplegia (one patient), and mental retardation (one patient).

**Discussion**

Is intrathecal streptomycin still necessary? The introduction of I.N.H. has virtually doubled the survival rate and there has been a natural tendency
to omit intrathecal treatment. There is ample evidence that cases recover without it (Smellie, 1954), and undoubtedly I.N.H. has made it possible to reduce the number of intrathecal injections. In company with others (Bernard, Duroux, Lotte, Jarniou, Bouvier, and Azorin, 1954; Taylor, 1954; Lorber, 1956), we have been slow to abandon a régime which has been producing progressively better results and we have therefore reduced intrathecal treatment slowly. In the present series all patients received at least 28 days' streptomycin with an 81% recovery rate. With a similar régime Lorber (1956) had 85% and Bernard et al. (1954) 93% recoveries. The evidence for and against intrathecal treatment is reviewed in the Lancet (1954) and the British Medical Journal (1955). We would support Lorber (1956) who discusses the problem and states that as yet there is no convincing evidence from the literature that it is unnecessary. Debré, Brissaud, Kaplan, Noufflard, Raynaud, and Naveau (1955) reserve intrathecal streptomycin for all children under 2 years and for all other patients who show any disturbance of consciousness. We have now reduced our routine minimum of intrathecal injections to two weeks but they are only stopped then if the general condition is satisfactory and the C.S.F. improving.

In the present series neither the length of history nor the C.S.F. sugar level bore any relationship to the amount of cerebral damage. This is due to vascular involvement (Cairns and Smith, 1952; Ritchie, Taylor, and Dick, 1953) and is determined in the early stages by chance. Obviously as the untreated disease progresses with increase of exudate the risk of vascular involvement becomes greater. The prognosis can be easily assessed by the patient's grading on admission. Of the 11 deaths in this series, 10 were in Group III patients, nine of whom had other detectable tuberculous lesions (Table III) and the only death outside this grade was in a patient in Group II who had miliary and spinal tuberculosis. In the absence of marked cerebral damage there should be virtually 100% recovery, with the occasional exception of the patient in whom meningitis is combined with extensive tuberculous lesions elsewhere. As has been so frequently stressed in the past, the need for early diagnosis is paramount.

Summary

A series of 58 cases of tuberculous meningitis is presented. There were 11 deaths (10 in patients graded in Group III) giving a survival rate of 81%.

Treatment was by intramuscular streptomycin and oral I.N.H. for a minimum period of six months combined with intrathecal streptomycin for at least 28 days. It is considered that intrathecal streptomycin is still indicated in the treatment of tuberculous meningitis, although with increasing experience it is suggested that this may safely be reduced to two weeks in certain cases.

We gratefully acknowledge much help given by Dr. James Macrae, resident physician at Ham Green Hospital, where these patients were treated.

References

British Medical Journal (1955), 1, 1200.
Lancet (1954). 2, 797. (Leading Article.)
Medical Research Council (1948). Lancet, 1, 582.