Tuberculous meningitis in children: a retrospective study of 79 patients, with an analysis of prognostic factors

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A study of 79 cases of tuberculous meningitis in children, with an emphasis on prognostic factors, was conducted by means of a review of hospital records and completion of a follow-up questionnaire. The survival rate was 62%. Stage 3 disease (with severe changes in the sensorium and often severe neurologic abnormalities) at the time of admission, age 3 years or less, associated miliary tuberculosis and delay in the initiation of therapy correlated significantly with poor outcome. Severe neurologic complications in the acute phase were also related to poor outcome and severe sequelae. General recommendations pertaining to treatment are made.

L'étude de 79 cas de méningite tuberculeuse chez l'enfant, accordant une attention particulière aux facteurs pronostiques, a été menée au moyen d'une revue des dossiers d'hôpital et d'un questionnaire évaluant les séquelles résiduelles. Le taux de survie a été de 62%. Une maladie de stade 3 (avec modifications graves de la conscience et, souvent, anomalies neurologiques graves) au moment de leur arrivée à l'hôpital, un âge de 3 ans ou moins, une tuberculose miliaire associée et un délai avant d'instituer le traitement ont été reliés de façon significative avec un mauvais dénouement. Les complications neurologiques sévères durant la phase aiguë ont aussi été reliées à un résultat sombre et à des séquelles sévères. Des recommandations générales relatives au traitement sont faites.

Tuberculous meningitis remains the most severe complication of tuberculosis. A review of 16 studies in the literature revealed that of 1412 patients with this complication, of whom only 18 were adults, 491 (34.8%) died.[1-16] The incidence of the disease has been steadily decreasing at our hospital: it fell from 0.67 per 100 admissions in 1957 to 0.04 in 1975. However, sporadic cases still occur and present special problems in management, particularly in the assessment of prognosis.

The purpose of this paper is to review clinical and therapeutic features of the 79 cases of tuberculous meningitis in children seen at hôpital Sainte-Justine in Montreal between 1953 and 1975.

Methods

Case records were retrieved from three sources: the hospital charts of all patients admitted with a diagnosis of tuberculous meningitis between 1953 and 1975 were reviewed, and from a screening of the pathology and microbiology records for the same period a few cases were added. To be included in the study a case had to meet the following requirements: a clinical picture compatible with that of the disease, and cerebrospinal fluid (CSF) findings of lymphocytic pleocytosis, a high protein concentration (more than 55 mg/dL) and a low glucose concentration (less than 2.5 mmol/L [45 mg/dL]). (A few patients with normal protein or glucose values were included because *Mycobacterium tuberculosis* was isolated from the CSF.)

We isolated *M. tuberculosis* from the CSF of 65 patients (82%). Acid-fast bacilli were grown from the gastric aspirate of three additional patients. Of the other 11 patients the diagnosis was confirmed by autopsy in 3, by chest roentgenography and skin tests in 3, and by chest roentgenography, chest roentgenography and a history of contact, and chest roentgenography, skin tests and a history of contact in 1 each; the 2 remaining patients were included in the study solely because their disease met the two basic requirements.

One patient from whose CSF *M. tuberculosis* was cultured was excluded from the study because his clinical course was not compatible with that of tuberculous meningitis, his CSF contained no cells, and the CSF protein and glucose concentrations were normal. He had miliary tuberculosis, which responded well to therapy.

Staging of the disease was done according to the criteria of Lincoln and Sewell.[17] Patients with stage 1 disease had general symptoms of infection, with lethargy, irritability, headache and vomiting. Stage 2 disease was characterized by signs of meningeal irritation and evidence of focal neurologic involvement. In stage 3 disease there were severe changes in the sensorium and often major neurologic abnormalities.

Follow-up data were obtained for all but four of the surviving patients. The mean duration of follow-up was 7.77 years (range less than 1 to 20 years). A questionnaire was completed concerning neurologic and psychiatric status, general physical health, and intellectual and social functioning (questions were asked about education, employment, social activities, behaviour problems, etc.).

To simplify presentation of the data, while retaining their predictive value for future life, sequelae were classified as minor (little or no mental retardation, minor neurologic deficits and minor behavioural problems, such that the individual could lead a relatively normal life) or major (gross mental retardation, severe neurologic deficits and complete dependence on others).

For statistical analysis of the results, we used the chi-square test with Yates' correction.

Results

General features

A total of 43 patients (54% of the 79) were less than 4 years old, 27 (34%) were less than 2 years old

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and 12 (15%) were less than 1 year old. Of the remaining patients 18 were 4 to 6 years old, 13 were 7 to 10 years old, and 5 were older than 10 years. There were 40 boys and 39 girls. All but six patients were French Canadian. Three patients were of Amerindian descent.

A history of contact with individuals having tuberculous disease was found in 36 cases. In most instances (22 of 36) either the mother or the father was the contact. Bacille Calmette-Guérin vaccine had been administered to 25 patients and had not been administered to 41; no information was available for the other 13.

The interval between onset of symptoms and hospitalization varied: 11% of the patients became ill less than 1 week before hospitalization, 22% were hospitalized after 1 week of symptoms, 32% were hospitalized after 2 weeks, and 29% were hospitalized after 3 weeks or more. In two patients symptoms developed during hospitalization. The interval between onset of symptoms and hospitalization was unknown in five cases.

The most common symptoms at the time of admission were vomiting (in 61%), fever (in 61%), headache (in 39%), lethargy (in 30%), behaviour problems (in 23%), convulsions (in 20%), coma (in 10%) and various neurologic abnormalities (in 9%).

At the time of admission 17 patients (22%) had stage 1 disease, 23 (29%) had stage 2 disease, and 35 (44%) had stage 3 disease. It was impossible to establish the clinical status at that time in four patients.

Throughout the years different methods were used to evaluate the skin reactivity of the patients; therefore, we have used the term "skin test" in a broad sense to encompass all tuberculin skin tests. Skin tests were positive in 34 of the patients, negative in 27 and not done in 18. Chest roentgenograms were performed in all but 2 patients, and were normal in 27; there was evidence of a primary complex in 24 patients, there were various alterations compatible with tuberculosis of the lungs in 14, and a pattern of miliary tuberculosis was seen in 12. Altogether, 18 of the patients had miliary tuberculosis; the diagnosis was made during life in 12 and at autopsy in 6. Half of these patients were less than 2 years old and a third were less than 1 year old. The mean protein concentration (± standard error) in the first specimen of CSF obtained after admission was 200.7 ± 40.7 mg/dL and the mean glucose concentration was 1.9 ± 0.1 mmol/L (33.6 ± 1.6 mg/dL). Mean protein concentrations were higher in patients with stage 3 disease (266.6 mg/dL) than in those with stage 1 disease (135.1 mg/dL) or stage 2 disease (164.3 mg/dL). This was because of a certain number of very high values in those with more advanced disease. Mean glucose concentrations were the same in all stages of the illness.

Treatment

Standard triple therapy consisting of streptomycin, isoniazid and para-aminosalicylic acid was administered to 44 patients. Streptomycin and isoniazid only were received by 24. One patient was treated with streptomycin, isoniazid and ethambutol, and two were treated with streptomycin, isoniazid, ethambutol and rifampin. One patient received isoniazid only, and two received streptomycin only; all three were considered to have been inadequately treated. Five patients received no therapy or died within 2 days of the beginning of therapy. Of the 71 patients who received adequate therapy, treatment was initiated in 16 after 3 days of hospitalization; this delay was due to failure to suspect meningeal tuberculosis. Most of these cases were managed as instances of bacterial or viral meningitis or encephalitis. Steroid therapy was administered to 42 patients. Seven patients received streptomycin and six others received steroids intrathecally.

Outcome

Of the 79 patients 49 (62%) survived. Table I shows outcome in relation to various factors. Stage 3 disease at the time of admission, age 3 years or less, associated miliary tuberculosis and delay in the initiation of treatment were significantly

Table I—Outcome of tuberculous meningitis in children in relation to various factors

Factor	No. of children		P value*
	Surviving	Dying	
Clinical stage of disease at time of admission			
Stage 1 or 2	31	9	< 0.02
Stage 3	17	18	
Age (yr)			
≤ 3	20	23	< 0.01
≥ 4	29	7	
Associated miliary tuberculosis			
Present	4	14	< 0.001
Absent	45	16	
Duration of illness before admission to hospital (wk)			
≤ 2	31	20	> 0.1
> 2	16	7	
Interval between admission and initiation of treatment (d)			
≤ 3	41	13	< 0.01
> 3	5	11	
Drugs given			
Streptomycin, isoniazid, para-aminosalicylic acid	29	15	> 0.1
Streptomycin, isoniazid	17	7	
Adequate others	3	0	
Steroids	27	15	
No steroids	22	7	
Bacille Calmette-Guérin vaccine			
Received	19	6	> 0.1
Not received	26	15	

*For chi-square test with Yates' correction.

related to increased mortality. The survival rate for patients receiving streptomycin, isoniazid and para-aminosalicylic acid was no better than that for patients receiving streptomycin and isoniazid only. Furthermore, the distribution of age and clinical stage of the disease was comparable in the two groups. When data for the 21 patients with delayed treatment and associated miliary tuberculosis were removed, the survival rate was 89% (25 of 28) for the group treated with streptomycin, isoniazid and para-aminosalicylic acid, compared with 74% (14 of 19) for those receiving streptomycin and isoniazid. These groups were too small for the data to be analysed statistically; however, the difference is not marked. Of the seven patients who received streptomycin intrathecally three had stage 3 disease at the time of admission to hospital and one had associated miliary tuberculosis and died; all the others survived with minor or no sequelae. Among the survivors were three patients who had major neurologic abnormalities in the acute phase (hydrocephalus in two and decerebration in one); two of them had minor sequelae and one had none.

Sensitivity testing of the isolated strains of *M. tuberculosis* from 18 patients was performed. Twelve of the strains were found to be susceptible to the antituberculosis drugs being used in that case. Three strains were resistant to isoniazid; one of the three patients died despite therapy with isoniazid and streptomycin, one patient received standard triple therapy and recovered slowly, though there were minor sequelae, and one patient, who had stage 3 disease at the time of admission and received isoniazid, streptomycin, rifampin and ethambutol, did very well. One patient, who had a strain resistant to isoniazid and para-aminosalicylic acid, was treated with isoniazid and streptomycin; he became decerebrate during his illness and had severe sequelae. One strain was resistant to para-aminosalicylic acid; after treatment with isoniazid, streptomycin and para-aminosalicylic acid the patient recovered. One patient had a strain resistant to that combination of drugs; he died after 1 day of therapy. Therefore, drug resistance was responsible for one death and for severe sequelae in one other patient.

Patients receiving steroid therapy were more severely ill than those not so treated; therefore we could not compare the two groups. Of the six patients who received steroids intrathecally three had stage 3 disease. One had associated miliary tuberculosis and died. Of the other five who survived, two became decerebrate during their illness and remained severely debilitated, and two of the other three had severe sequelae. Skin test reactivity was not an important prognostic factor; however, patients with negative tests were more often treated with undue delay and consequently had an increased mortality. There was no relation between the protein or glucose concentration in the CSF and outcome.

We re-evaluated our data to determine if any two of the factors adversely affecting prognosis were interrelated.

Clinical stage: Age and clinical stage were interrelated to the extent that patients with stage 3 disease were more often younger (Table II). However, five of the seven deaths in the older group were in patients with stage 3 disease. Nine of the 18 patients with miliary tuberculosis had stage 3 disease and all died (Table III). This fact is largely responsible for the poorer outcome of stage 3 disease. Treatment of stage 3 disease was not delayed.

Table II—Outcome in relation to patient's age and clinical stage of disease at time of admission to hospital

Age (yr) and clinical stage of disease	No. of children		
	Total	Surviving	Dying
≤ 3			
1	7	4	3
2	12	7	5
3	22	9	13
?	2	0	2
Total	43	20	23
≥ 4			
1	10	9	1
2	11	11	0
3	13	8	5
?	2	1	1
Total	36	29	7

Table III—Outcome in children with tuberculous meningitis and associated miliary tuberculosis

Clinical stage of disease	No. of children	
	Surviving	Dying*
1	1	3 (3)
2	3	2 (0)
3	0	9 (5)

*Number of patients whose illness was diagnosed before death in parenthesis.

Age: Patients aged 3 years or less had stage 3 disease more often at the time of admission. This partly explains the poorer prognosis of this age group. However, there were more deaths in younger patients with stage 1 or 2 disease than in their older counterparts (Table II). Although 67% of the patients with associated miliary tuberculosis were in the younger group, a significant difference in outcome between the two age groups remained after data for these patients were removed. There was no increased delay in treatment of the younger group.

Miliary tuberculosis: This subgroup of 18 patients tended to be younger, although there was no marked difference in age distribution (67% of the subgroup v. 54% of the entire group were 3 years of age or younger). Only one of the seven older patients survived. In this subgroup, outcome was poor in all stages of the disease, although stage 3 had the worst prognosis. Of the 13 patients who received treatment 5 did so after 3 days in hospital. Four patients died early, so therapy could not be assessed, and one patient received inadequate therapy. Of the eight patients who received adequate and early therapy, only three survived.

Delay in initiation of therapy: There was no relation between age or clinical stage and delay in initiation of therapy. Of the 16 patients whose treatment was delayed 5 had miliary tuberculosis and 4 of them died. However, elimination of the data for patients with miliary tuberculosis left a significant difference ($P < 0.01$) between those treated early and those treated late.

Complications and sequelae

Severe complications developed in 28 patients during hospitalization:

both of the 2 patients who became decorticate died, 13 of the 18 who became decerebrate died (4 of the 5 survivors had severe sequelae), and 4 of the 8 patients with hydrocephalus died (2 of the survivors had severe sequelae).

Of the 49 survivors 18 had no sequelae, 15 had minor sequelae (4 had behaviour problems, 2 had learning problems, 2 had epilepsy, 2 had low-normal intelligence, and 1 each had sexual precocity, unilateral deafness, diabetes insipidus, unilateral hemiparesis or severe obesity) and 12 had major sequelae (8 had moderate to severe mental retardation, and 1 each had bilateral deafness, mental retardation with defective coordination of movement, hemiplegia with slight mental retardation or spastic quadriparesis). The long-term outcome was unknown for four patients, but three probably had minor sequelae or none at all.

Major sequelae were related to age: 7 (35%) of the 20 patients in the younger group of survivors had major sequelae, compared with 5 (17%) of the 29 patients in the older group. Patients with stage 3 disease were more likely to have major sequelae: 5 (29%) of the 17 patients were permanently debilitated by the disease, compared with 6 (19%) of the 31 with stage 1 or 2 disease.

Six (22%) of the 27 survivors who received steroids had major sequelae, compared with 6 (27%) of the 22 survivors who did not receive steroids; however, individuals who received steroids were more severely ill at the onset of the disease.

Patients who received only streptomycin and isoniazid did not have more sequelae than other survivors.

Discussion

Tuberculous meningitis still has a high mortality, despite early diagnosis and modern therapy. Of 35 patients seen since 1963 at our hospital 10 have died (mortality 29%). Since 1971 we have seen nine patients, of whom six had stage 3 disease at the time of admission and two had associated miliary tuberculosis. One third of these patients died.

Our patient population was comparable in severity of illness to that of Wasz-Höckert and Donner,[2] as is reflected by similar mortality in the two studies (38% and 44% respectively). In contrast, four studies of less severely affected populations discovered lower mortality (32.4%, 18.6%, 20% and 23.7%).[1,6-8]

Chest roentgenograms showed no evidence of tuberculosis in 27 (34%) of our patients. This finding is similar to that of Zarabi, Sane and Girdany:[18] of 180 children with tuberculous meningitis 43% had normal chest roentgenograms.

One of the problems in treating this disease, assessing prognosis, is due in part to the slow progress of the disease and its late response to treatment. We have confirmed that certain factors are important in determining outcome. Low age is associated with a poor prognosis. This was shown in 1960 by Lincoln, Sordillo and Davies[1] and in 1963 by Wasz-Höckert and Donner.[2] However, in contrast to the former and in agreement with the latter, our study has shown that the increased mortality extends to 3-year-olds. Numerous studies,[1,2,8,12,13,16] including ours, have shown a correlation between clinical stage of the disease at the time of hospital admission and outcome. However, this correlation was much weaker in our study when we removed the data for patients with miliary disease, and it failed to attain statistical significance.

We have found a correlation between the presence of accompanying miliary tuberculosis and increased mortality, as have Lepper and Spies.[19] However, such a correlation was not found by Lincoln and colleagues[1] or by Weiss and Flippin.[20] The increased mortality observed by us was due partly to the fact that six of our patients were found only at autopsy to have disseminated tuberculosis. However, of the 12 patients in whom the diagnosis was made during life only 4 survived. This suggests that, although there are probably patients with meningitis and unsuspected miliary tuberculosis who survive, the presence of miliary tuberculosis proven roentgenographically is a bad prognostic factor. This is surprising since miliary tuberculosis without meningitis has a good prognosis in children.[21,22] Our search for other factors associated with miliary tuberculosis to explain its apparent influence on outcome was unproductive.

Delayed treatment was associated with a poor prognosis; in our study, treatment was often initiated 4, 5 or 6 days after admission. This correlation suggests that rapid diagnosis and early treatment are essential in ensuring a high survival rate, an implication not confirmed by the study of Weiss and Flippin.[20] We cannot explain this discrepancy.

Hydrocephalus and decerebrate and decorticate rigidity were related to poor survival and severe sequelae. Udani, Parekh and Dastur[23] have shown that decerebrate rigidity reflects advanced disease with important pathologic lesions. Antecedent vaccination with bacille Calmette-Guérin was not associated with decreased severity of the disease, contrary to the report by Paul.[24] However, no data on skin test reactivity after vaccination were available for our patients, and it is possible that vaccination failed in some of these children.

Although this retrospective study could not fully evaluate the relative effectiveness of a given therapeutic agent, it has provided partial evidence that para-aminosalicylic acid is not very effective in the treatment of tuberculous meningitis. Rifampin, a new antituberculosis drug, is a prime candidate to replace it. Rifampin can penetrate into CSF[25] and, in combination with isoniazid, has been shown to be superior to streptomycin, isoniazid and para-aminosalicylic acid in the treatment of tuberculous meningitis.[10] Other drugs of potential value are ethambutol,[26] pyrazinamide and ethionamide.[27] Further clinical trials will determine the most effective combinations.

We could not evaluate steroid therapy in great depth because the patients who received such treatment had more advanced disease. However, we believe they are useful in gravely ill patients, particularly if there is a cerebrospinal block, asso-

ciated or not with decerebrate rigidity.[3] Cerebral edema is another indication.[28] Escobar and colleagues[9] have shown increased survival in patients receiving steroids as part of their treatment. However, Weiss and Flippin[20] have not found this to be the case.

Twelve of our 49 survivors had severe sequelae; this finding is comparable to that of other authors.[2,8] We found age and clinical stage of the disease at the time of admission to be related to severity of the sequelae, as was also noted by Wasz-Höckert and Donner[2] and by Lorber.[29] However, Todd and Neville[30] did not find such a correlation.

Tuberculous meningitis is becoming increasingly rare. Continued awareness of its existence, rapid establishment of diagnosis, and early therapy will remain the only means of ensuring a satisfactory prognosis.

Isoniazid and rifampin have proven effective in the treatment of tuberculous meningitis,[1,2,10] and should form the mainstay of an adequate drug regimen. One or possibly two additional drugs should be given to ensure a strong bactericidal combination[27,31] and to cover possible resistance to one of the drugs.[7] In one of our patients quadruple therapy circumvented isoniazid resistance. Streptomycin and ethambutol are usually used for this purpose. Steroids should be given to patients with severe disease and major neurologic abnormalities; their use in all patients is still controversial.[32]

Intrathecal therapy is no longer used at our hospital. A controlled study[5] failed to show convincingly that this method of treatment improved the patients' outcome, and, although it is recommended by some,[33] it has not gained general approval in the North American literature. Seven of our patients received streptomycin intrathecally in addition to adequate systemic therapy, and all but one recovered. This suggests that intrathecal streptomycin therapy may be of value, at least in some patients; further controlled clinical trials are needed to establish precise indications for its use. The same is true for intrathecal administration of steroids, although our results in six patients were rather poor.

These therapeutic recommendations are admittedly not all based on results of controlled clinical trials. There is a need for such studies comparing different combinations of antituberculosis drugs in the systemic treatment of tuberculous meningitis. The role of steroids should be further explored to establish clear indications for their use. Finally, an answer to the question of the value of intrathecal therapy would be welcomed.

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