

TUBERCULOUS MENINGITIS TREATED WITH STREPTOMYCIN

FOLLOW-UP OF SURVIVORS FOR A MINIMUM OF TWO AND A HALF YEARS

BY

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In February, 1949, two of us (J. R. and A. F. M.) reported the results of the treatment of 54 patients for tuberculous meningitis. These patients were admitted to a special unit during the period July, 1947, to May, 1948. The minimum observation period at the time of that report was eight months (Rubie and Mohun, 1949). The survivors have now been observed for a minimum period of two and a half years, and it is felt that a report on the original series after this longer period would be of value. The maximum observation period is three and a half years.

Results

The results are summarized in the Table. The original 18 survivors have been reduced to 16 (30%), two having died. Three patients relapsed, but have recovered after further treatment.

The periods for which streptomycin was given for the relapses are shown in the Chart. The daily dose was the same as mentioned in the previous report.

Sequelae shown by the survivors are deafness in two children (partial in one), a minimal hemiplegia in one child, retarded development in one, and an intellectual defect in one.

Audiometric and vestibular tests have been carried out on 14 of the 16 survivors. All showed complete loss of vestibular response during caloric tests, yet none of them show clinical ataxia in a good light. Some patients, however, were slightly ataxic with the eyes closed or in the dark. Audiometric tests revealed a marked hearing loss in Case I and a loss up to 50 decibels in Case 11. In the remainder the audiograms were normal.

Later manifestations of non-meningeal tuberculosis, presumably due to sporadic haematogenous dissemination of tubercle bacilli, have occurred in two recovered cases (Nos. 1 and 11). These have not been accompanied by any evidence of recrudescence of meningitis.

Although the number of cases is small, there is no evidence to show that patients who present radiological

Details of the 18 Original Survivors (December, 1950)*

Case No.	Age at Onset (Years)	Stage on Admission	Chest X-ray	Period of Observation from Start of Treatment (Months)	Method of Treatment	Course
1	4 6/12	E	P.C. Mil.	41	I.T. and I.M.	Latest C.S.F. normal, but previous small fluctuations in cells and protein. Deaf. Ataxia not now apparent. Developed synovial tuberculosis of left wrist 28 months after onset of meningitis; this is responding to orthopaedic treatment
2	4 7/12	M	Mil.	41	" "	C.S.F. normal. Full recovery. Ataxia not now apparent. Attends normal school
3	8 8/12	E	P.C.	41	I.M.	Latest C.S.F. normal, but previous small fluctuations in cell count. Full recovery. Tuberculous left knee was treated with a splint (now discarded) for 3 years from onset of meningitis. Attends normal school
4	6 1/12	M	"	41	I.T. and I.M.	C.S.F. normal. Full recovery. Attends normal school
5	6 6/12	E	Nil	40	" "	C.S.F. normal. Full recovery. Attends normal school
6	3 4/12	E	P.C.	39	" I.M.	Latest C.S.F. normal, but previous small fluctuations in cell count. Full recovery. Tuberculous spine was treated with a spinal jacket (now discarded) for 3 years from onset of meningitis. Attends normal school
7	12 11/12	M	Nil	39	I.M.→I.T.	Full recovery. C.S.F. showed a persistently raised protein (50–100 mg. per 100 ml.). Attended a school for backward children before illness and has returned to same school. No evidence of deterioration
8	15 6/12	E	Mil.	39	I.T. and I.M.	C.S.F. normal. Full recovery
9	10 10/12	M	P.C.	37	" "	Latest C.S.F. normal, but previous small fluctuations in protein content. Physical and mental development retarded in comparison with twin sister
10	10 4/12	A	Nil	35	" "	C.S.F. normal. She shows an intellectual defect and maladjustment of hysterical type, possibly precipitated by tuberculous meningitis
11	11	E	Mil.	33	" "	Full recovery, with normal C.S.F. 11 months after onset of original illness. Relapse 8 months later followed by full recovery after further treatment, with normal C.S.F. 12 months later (31 months after onset of original illness). During the final period of intramuscular treatment she developed a tuberculous abscess over the sternum which resolved satisfactorily. Partial deafness
12	17 8/12	E	Nil	18	" "	Previously reported as full recovery with normal C.S.F. Relapsed 13 months after onset of original illness and died 5 months later in spite of further treatment. Necropsy revealed a cortical tuberculoma
13	10	M	Nil	32	" "	Full clinical recovery. C.S.F. has shown fluctuation in cells (3–26 per c.mm.) and in protein (60–160 mg. per 100 ml.); it has not been entirely normal at any single examination. Attends normal school
14	6	M	Nil	32	" "	C.S.F. normal. Residual minimal right hemiplegia. Attends a normal school
15	5 6/12	E	Mil.	32	" "	C.S.F. normal. Full recovery. Attends a normal school
16	10 3/12	E	"	31	" "	Previously reported as full recovery with normal C.S.F. (11 months). Relapsed 3 months later and responded to further treatment with full recovery and normal C.S.F. 14 months later (28 months after onset of original illness). Attends normal school
17	5 1/12	M	P.C.	13	" "	C.S.F. never became normal. He died with a recrudescence of the disease 13 months after onset of illness
18	4 11/12	E	"	31	" "	Previously reported as full recovery with normal C.S.F. (9 months). Relapsed 4 months later and responded to further treatment with full recovery and normal C.S.F. 14 months later (27 months after onset of original illness). Attends normal school

E = Early case. M = Middle case. A = Advanced case. P.C. = Primary complex. Mil. = Miliary disease of lungs. I.T. = Intrathecal streptomycin. I.M. = Intramuscular streptomycin. I.M.→I.T. = Intramuscular followed by intrathecal streptomycin. I.T. and I.M. = Intrathecal and intramuscular streptomycin together.

* At April, 1951, the condition of the survivors is unchanged.

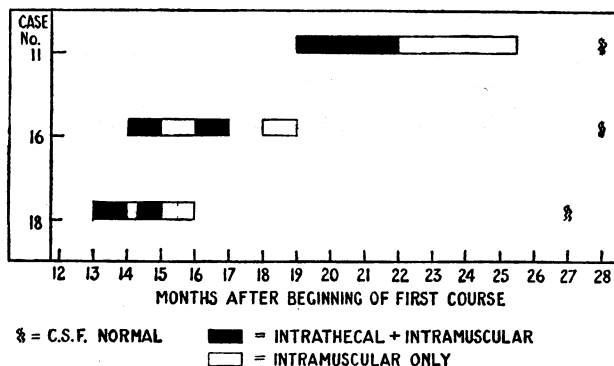


Chart showing periods during which streptomycin was given for relapse. The criteria of C.S.F. normality have been: cells—not more than 5 per c.mm.; protein—not more than 40 mg. per 100 ml.; chlorides—not less than 720 mg. per 100 ml.; sugar—not less than 45 mg. per 100 ml.

signs of miliary tuberculosis of the lungs associated with meningitis are subsequently more liable to relapse.

Conclusions

A relapse may occur in cases of tuberculous meningitis after full clinical recovery and return of the cerebrospinal fluid (C.S.F.) to normal. No precipitating cause for relapse has been found.

Occasional slight abnormalities of the C.S.F. up to two years after cessation of all treatment may be unaccompanied by any other evidence of activity. The significance, if any, of these variations can be assessed only by a further period of observation, the length of which has not yet been determined. We therefore do not feel able to regard a patient as finally cured and requiring no further observation even after two and a half years from the cessation of streptomycin treatment.

Summary

A follow-up report is presented on the condition of the survivors in a series of cases of tuberculous meningitis previously reported.

Of the 18 original survivors, two have died, and three have relapsed but recovered after further treatment. Two developed non-meningeal tuberculous lesions which responded to treatment. The survival rate has been reduced to 30% (16 cases).

Slight variations in the C.S.F. of the survivors have been found, but their significance could not be determined. A further period of observation is necessary.

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REFERENCE

Rubie, J., and Mohun, A. F. (1949). *British Medical Journal*, 1, 338.

The Minister of Health (Mr. H. Marquand) recently visited a blood-donor session at a London hospital and himself gave a pint of blood. In a short speech he remarked that hospitals to-day used nearly 1,000 pints of blood a day, a fiftyfold increase on pre-war. Another 200,000 blood donors were needed to meet all the demands now being made on the National Blood Transfusion Service.

ORF IN LONDON

BY

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The word "orf" is derived from the Saxon for cattle; it is now applied to contagious pustular dermatitis, a malady of sheep that is well recognized by those who deal with these animals.

Hansen (1879), Hatzios (1929), Peterkin (1937), Schoch (1939), and others have described the lesions of orf in man, and the condition is now well recognized as being common in many sheep-rearing localities; in southern England, and especially in London, it has rarely been seen. For this reason, and because the disease is likely to be mistaken for a simple pustular infection, the following cases are recorded, all having occurred within three months (November, 1950, to January, 1951) in London.

Natural History

In sheep, orf is characterized by ulcerative and pustular lesions of the skin and mucous membranes. It occurs particularly in lambs under 1 year old. The mortality rarely exceeds 1% (National Veterinary Medical Association publication, 1944). Human orf follows contact with infected animals, whether dead or alive. In the latter the saliva seems to be particularly infectious, and there is evidence that dried saliva crusts may also harbour the infection for several months (Glover, 1929). The incubation period has never been accurately assessed, but it is short, and is probably between three and seven days.

The infected person usually has a single lesion situated on the arm or hand, or occasionally it may be on the face; sometimes multiple lesions are seen (Blakemore, Abdussalam, and Goldsmith, 1948).

The lesion consists of a raised nodule, 1–3 cm. in diameter, which usually is ulcerated at its summit. The shallow ulcer is surrounded by dead, white, soggy skin, and the whole gives the appearance of a granuloma in the centre of a blister or pustule. When explored, as it not infrequently may be, pus is not obtained, and only a little blood exudes. Pain is slight and general toxic symptoms are mild or absent; lymphangitis and regional lymphadenopathy may be present; but all are less pronounced than would be expected if the lesion were of pyococcal origin.

The infection is self-limiting: resolution occurs in five to eight weeks, and is completed with remarkable rapidity when once it starts.

The causative organism is a virus which has been isolated by several workers and found to be morphologically (by electron microscopy) and immunologically identical with the virus found in contagious pustular dermatitis of sheep; further, the disease has been experimentally transmitted to a human volunteer (Blakemore, Abdussalam, and Goldsmith, 1948). Lyell and Miles (1950) reported having cultivated the virus from man on living chick embryos; subsequently they infected the lamb with the virus, the animal developing typical contagious pustular dermatitis. Thus, instead of having merely circumstantial evidence of the connexion between orf in man and the infection in sheep, the relationship can now be regarded as proved.