Streptomycin in Tuberculous Meningitis
Report of a Case*

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The treatment of tuberculous meningitis with streptomycin is under critical observation at the present time. The advent of this new drug was greeted with much enthusiasm but further clinical experience on a greater number and variety of cases has led to better appreciation of its merits and dangers. It is true that in most cases of tuberculous meningitis the immediate effects of streptomycin therapy have been so striking as to promise hope of recovery. On the other hand many of these hopes have not materialized.

The following is a report of a case of proven tuberculous meningitis that has been treated with streptomycin.

The patient, F. McK., a 34 year old, white male, entered the hospital on the 21st of June, 1946, with the diagnosis of meningitis of unknown origin. His chief complaints were headache, blurred vision, malaise, nausea and vomiting. These had been ushered in a few hours previously by a single shaking chill followed by a temperature rise to 101 degrees F.

He gave a history of known tuberculosis of the right lung which was discovered in July 1945 and was responding satisfactorily to pneumothorax therapy. In December of 1945 a small amount of fluid was aspirated from the right side of his chest. At that time he also developed ascites and 2000 cc. of straw-colored peritoneal fluid were removed. He gave a history of drinking unpasteurized milk. He did not use alcohol and never had catarrhal jaundice. Sputum has been negative for acid-fast bacilli since April of 1946. The last pneumothorax refill was administered five weeks prior to his present illness. There were no other pertinent findings in his past medical history and his family history was not significant.

Physical examination revealed a toxic, irritable white male, complaining of severe headache and nausea. Speech was thick and difficult. Response to verbal stimulation was slow and labored. He could not write or read his own name. He exhibited nuchal rigidity, absent deep tendon reflexes and positive Babinski, Chaddock, Gordon and Oppenheim signs. Tuberculous meningitis was considered the most likely diagnosis but considerable laboratory work was done to rule out other conditions.

The agglutination series was negative, malaria studies were negative, the icteric index was 5 and the cephalin flocculation showed nothing abnormal. On admission the blood count showed 84.4 per cent hemo-

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globin, 4,250,000 RBC, 6,000 WBC, with a normal differential count. Urinalysis and serologic studies were negative. The spinal fluid showed no organisms at first but the second tap revealed pellicle formation and a few acid-fast bacilli were seen. These were later cultured. The spinal fluid was cloudy, globulin was greatly increased, the cell count was 139 with 80 per cent polymorphonuclear cells and 20 per cent lymphocytes; dextrose was 37 mgm. per cent and the tryptophane test was positive. The sputum was repeatedly negative for acid-fast bacilli.

The temperature on admission was 102 degrees F., the pulse was 100 and the respiratory rate 20 to 25. Penicillin therapy was immediately started but had no effect. Blurring of vision became more marked and difficulty with urination developed. The temperature continued to rise daily to 102 degrees F. and projectile vomiting made its appearance. The patient’s condition, heretofore, critical, now became grave.

On the 28th of June, eight days after admission, streptomycin therapy was instituted and on the 30th of June the penicillin was discontinued. Initially the patient was given 2½ grams daily in divided doses by the intramuscular route and 100,000 units intrathecally every other day. His general condition immediately started to improve. During the first month the temperature gradually subsided. The number of cells in the spinal fluid diminished considerably and the fluid itself appeared clearer although a pellicle still formed on standing. Headache, nausea and vomiting persisted but were not so bothersome. The patient was frequently flushed after intrathecal injection of the drug and complained of shooting pain down the legs. This was also accompanied by a transient increase in severity of the headache and dizziness.

Gradually the nuchal rigidity decreased but did not disappear completely until 4 months later. All other neurological signs disappeared with the exception of ankle clonus which persisted for five months.

The second month of treatment was marked by further clinical improvement which was very slow and steady. Some of the signs of streptomycin toxicity made their appearance. These were: slight deafness, tinnitus, pain in the legs on intrathecal administration, nausea and varying degrees of hyperaesthesia. This called for a change of dosage and thereafter the patient received 100,000 units of streptomycin every four hours intramuscularly, while continuing on the same intrathecal dose. The above-mentioned signs then lessened.

In the third month of treatment the drug was discontinued for five days because the patient had improved so greatly and the test period was over. Vomiting began three days after discontinuance accompanied by a rise in temperature. Streptomycin therapy was quickly resumed in the same dosage but the vomiting persisted and became very severe. The white blood cell count remained normal and the number of cells in the spinal fluid rose only slightly. The sugar content of the fluid remained at 27 mg. per cent and the chlorides at 528 mg., the cobweb coagulum still being present. No organisms could be recovered or cultured. Intractable vomiting now became a great problem. Intravenous fluids and blood transfusions were frequently given. Amino acids or plasma by vein invariably produced severe reactions. The patient became dehydrated and lost flesh rapidly. The blood chlorides sank to 2.47. This, in combination with a blood pressure of 90 over 72, weakness and vomiting prompted the empirical use of adrenal cortical extract and salt. Unfortunately the laboratory was not equipped to do blood sodium or potassium determin-
Reactions. Atropine sulphate did not relieve the vomiting and it was only after a Miller-Abbott tube was passed through the pylorus and hourly jejunal feedings given, that the patient was brought under control. After one week the blood pressure and chlorides rose to normal levels so the administration of adrenal cortical extract was stopped. The tube remained in situ for ten days. Then the patient began to eat well enough to warrant its removal. Slowly he began to regain the ground he had lost. He no longer complained of headache but did become quite dizzy upon raising the head. Vomiting attacks gradually decreased in frequency and severity until occasional morning nausea was all that was noted.

By the end of the fifth month the patient had shown much clinical improvement. Vomiting was very infrequent and only occurred after breakfast. Fluids and most solid foods were very well tolerated. He looked forward to recovery with amazing confidence characterized by a cheerful and alert mental attitude. Speech was normal and writing improved rapidly. Further progress was evidenced by a daily walk about the room despite dizziness. He used a bedside commode. Because of occasional diplopia and somewhat hazy vision several eye consultations were requested. All these examinations were negative. During the course of the month his weight was not quite maintained and his muscles remained flabby. Whenever streptomycin was administered intrathecally the same shooting pain was noticed in the underlying leg and in the scrotum.

The laboratory now reported a slightly xanthochromic spinal fluid with only eighteen cells, increased globulin and a normal dextrose content of 50 mg. per cent. A pellicle still formed on standing but yielded no acid-fast bacilli on culture or guinea pig inoculation. The blood count continued to show a moderate anemia and the sedimentation rate was 16 mm. per hour. The NPN and blood sugar were normal and the total plasma proteins were 7.4 with 3.63 globulin. The only persistent neurological finding was a mild degree of ankle clonus. The temperature varied from 98.0 to 99.6 degrees F.

Streptomycin was continued in the same dosage throughout the sixth month and clinically the patient improved in spite of the spinal fluid findings. He felt well even though dizziness persisted whenever he stood upright. Toward the end of the month he was walking to the bathroom. His gait was so unsteady that he had to support himself by touching or holding nearby objects. Ankle clonus decreased. A good appetite was responsible for a two-pound gain in weight. Diplopia and hazy vision remained about the same. All tests of kidney function were satisfactory. The red cell count and hemoglobin rose slightly but the white cell count was somewhat low at 4,500. No eosinophiles were present. The sedimentation rate varied from 9 to 15 mm., the spinal fluid sugar rose to 90 mg. per cent, the cells reached 200 and the protein increased to 108. The patient's temperature during this month frequently reached 99 and occasionally 100 degrees F. Sputum remained negative for acid-fast bacilli.

A milestone in the history of the case was reached in the seventh month for it was then that streptomycin therapy was finally discontinued. The patient began to complain of increasing pain in the hips upon intramuscular injection and so it was decided on January 10, 1947 that this mode of administration be stopped. Intrathecal injections
were continued as before but it quickly became apparent that this also was causing increasing distress. The pain would now begin as soon as the needle was introduced whereas previously it had never occurred until the drug was injected. In addition it was becoming more difficult to perform an adequate puncture due, presumably, to the local changes that had taken place in the tissues. On the 15th and 18th of the month the patient developed transient paraplegia and a transient loss of bladder function. For this reason intrathecal injections of streptomycin were discontinued. Since that time he has received none of the drug whatsoever.

A neurological examination now revealed atonia of all muscles, particularly of the lower extremities. The muscles were flaccid and weak. All deep tendon reflexes were active and no sensory disturbances were present. Ankle clonus was no longer apparent. A caloric stimulation test was normal for both ears but a whispered voice test showed loss of the ability to hear high tones. The patient had no difficulty in hearing the normal speaking voice.

It is interesting to note that prior to the discontinuance of streptomycin, particularly in the last month of treatment, the temperature frequently reached 100 and occasionally 100.6 degrees F., but as soon as the drug was stopped the temperature fell and since that time has only once been above 99.2.

The patient was cheerful and boasted of a good appetite. Clinically he gained with amazing rapidity. The most remarkable occurrence was a 14-pound gain in weight during the seventh month of treatment. Diplopia and hazy vision gradually decreased. His gait was still very unsteady.

The last spinal fluid examination prior to termination of the drug therapy showed 24 cells, 49 mg. per cent sugar and a negative tryptophane test. Cultures continued negative for acid-fast bacilli. Other laboratory data which included complete blood counts, urinalyses, bromsulfalein, urea clearance, NPN, creatinine and sugar were all within normal limits.

In the middle of February, one month after discontinuance of the streptomycin, a change was seen in the patient's condition. Headaches became more severe and the customary cheerfulness changed to apprehension. Suspicions were aroused when he gained six pounds in one week in spite of the fact that he was not eating with the usual relish. He complained of weakness and scanty urine. Physical examination revealed a moderate amount of fluid in the abdomen. This was not tapped. A complete physical and laboratory work-up showed that the fluid was not due to constrictive pericarditis or interference with portal circulation. Tuberculosis was considered the most likely cause but actual proof was lacking. Within two weeks spontaneous diuresis occurred with resulting loss of ascites and a 10-pound loss of weight. This episode is interesting in view of the fact that the patient was reported to have had ascites in December of 1945. For the remainder of the month he felt well except for an increase in the frequency of his headaches. These would now occur about three times a day, at 2 a.m., 11 a.m., and 3 p.m., which coincided with sleep or rest hours. He obtained relief only by getting out of bed and walking about.

During the second month after termination of drug therapy clinical improvement continued. There was no evidence of fluid in the abdomen.
He gained weight at a more normal rate, about a pound or two a week. The frontal headaches that appeared during the reclining hours persisted in varying degrees of intensity and they were still relieved by standing up and walking. Dizziness was practically absent and deafness was not noticed in ordinary conversation. His gait had improved so remarkably that he could walk about without support. The diplopia and hazy vision had decreased to such an extent that he could read a newspaper or write a letter with apparent ease.

The patient showed gradual improvement during the next few months. Slowly but steadily his activities were increased without untoward effect. Walking to the washroom helped him regain the muscular tone of his lower extremities. A certain degree of ataxia was present but became increasingly difficult to demonstrate. The headaches decreased in number and intensity until they disappeared. On the fourth of July, 1947, he suffered an acute attack of appendicitis and at the time of operation the appendix had ruptured due to the patient's refusal to accept early surgery. Microscopic examination of the appendix and culture of drainage were negative for acid-fast infection. Examination of the peritoneal cavity at the time of operation failed to reveal any evidence of tuberculosis. This is important in view of the patient's past record of recurrent episodes of ascites.

Recovery from this operation was rapid with gradual cessation of drainage and thorough healing of the wound. Convalescence was uneventful. By the end of the month the patient was out of bed again and shortly reached his previous level of ambulatory efficiency.

He remained in the hospital three months following his appendectomy, during which time no further improvement was noted. He appeared perfectly normal except for slight ataxia and a moderate degree of high tone deafness. Tests of vestibular function by the Kobrak method of caloric stimulation were within the normal limits. His ordinary gait was without flaw but he had difficulty walking with his eyes closed. Neurological tests failed to reveal any other dysfunction. In September of 1947 after stating that he "never felt better in my life," he left the hospital against medical advice. His departure occurred fifteen months after admission and eight months after discontinuance of streptomycin therapy.

Due to the fact that he returned to the hospital about twice a month for pneumothorax refills, we were able to follow his case quite adequately. He has been observed for six months in this manner and he is still in a state of remission. He appears normal in all respects but when specifically questioned, it is learned that slight ataxia persists as evidenced by inability to walk along a narrow plank and a feeling of insecurity while driving a car fast. Adequate financial compensation has so far spared him the necessity of working. In January 1948 he married and is at present leading a happy home life.

SUMMARY

A case of a man with proven tuberculous meningitis is presented. After initial streptomycin therapy was instituted, he showed marked clinical improvement. When the drug was discontinued he suffered a severe relapse. Renewal of streptomycin therapy was barely able to stave off a fatal termination but after four additional months of treatment he slowly progressed to a point
where it was deemed feasible to discontinue the drug. He received about 160 grams of streptomycin in seven and one-half months by the intramuscular and intrathecal routes. His course after treatment was marred by one relatively short, self-limited episode of ascites and an attack of acute appendicitis for which an appendectomy was performed. Symptomatic therapy played a large part in combating his disease. Certain findings which persisted for several months after therapy but which eventually disappeared completely, were headache and haziness of vision. Other findings which improved after therapy but which still persist are slight ataxia and high tone deafness. The patient seems to be adequately compensating for his vestibular dysfunction. All during his illness and up to the present time he has been receiving pneumothorax refills. The chest lesion shows no change and the sputum is still negative. Twenty-two months have passed since the onset of his disease, the last six of which he has spent at home with no ill effects.

Considering the percentage of fatality in tuberculous meningitis, even since the advent of streptomycin, it is felt that this patient has progressed remarkably, possibly further than any that have been treated with this drug, and it is hoped that as time goes on the possibility of a relapse will become even more remote. October 15, 1948, still well clinically.

RESUMEN

Se presenta el caso de un hombre con meningitis tuberculosa comprobada. Después de haberse iniciado la estreptomicinoterapia el paciente mostró decidida mejoría clínica. Cuando se descontinuó la droga, sufríó una recaida grave. La reanudación de la estreptomicinoterapia a penas evitó un desenlace fatal, pero después de cuatro meses adicionales de tratamiento progresó poco a poco hasta tal punto que se creyó posible descontinuar la droga. El paciente recibió, aproximadamente, 160 gramos de estreptomicina por las vías intramuscular y cefalorraquidea en siete meses y medio. Su curso después del tratamiento fue complicado por un episodio relativamente corto de ascitis, que terminó solo, y por un ataque de appendicitis aguda que necesitó que se le hiciera una appendicectomía. La terapia sintomática desempeñó un gran papel en combatir la enfermedad. Dolores de cabeza y vista enfoscada fueron hallazgos que persistieron por varios meses después de la terapia, pero que al fin y al cabo desaparecieron por completo. Otros hallazgos que mejoraron con la terapia, pero que todavía persisten, son ataxia leve y sordera para los tonos altos. El paciente parece estar igualando adecuadamente su disfunción vestibular. Durante toda su enfermedad y hasta la fecha ha estado recibiendo insu-
flaciones de neumotórax. La lesión torácica no ha variado y el esputo continúa negativo. Han pasado veintidós meses desde el comienzo de su enfermedad, los últimos seis de los cuales los ha pasado en su casa sin mal efecto alguno.

Tomando en consideración el porcentaje de desenlaces fatales en la meningitis tuberculosa, aún desde el advenimiento de la estreptomicina, se opina que este paciente ha progresado extraordinariamente, posiblemente más que ninguno otro que ha sido tratado con esta droga, y se abriga la esperanza de que mientras más tiempo pase menor será la posibilidad de que sufra una recaída.