THE TREATMENT OF TORULA MENINGO-ENCEPHALITIS WITH AMPHOTERICIN B*

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(Received for publication August 2, 1957)

The eventual course of meningo-encephalitis caused by Cryptococcus neoformans is well known. Any agent that improves or arrests the course of this illness should be brought early to the attention of those physicians who see and diagnose this infection. Cryptococcosis, torulosis, and European blastomycosis refer to the same mycotic disease caused by the Cryptococcus neoformans. This fungus is widespread in nature and reports of the disease it produces have come from nearly all areas of the world. The greatest number of cases have been reported from the United States and Australia. This infection, which fails to cause a very great tissue response, is considered to be air-borne, with the reservoir being in the soil. Although the infection is air-borne, it is disseminated from the lungs through the blood stream. The central nervous system is particularly susceptible and this involvement is usually manifest as a meningo-encephalitis. Once there is involvement of the central nervous system, a fatal outcome is almost certain.2

Historically the first record of the identification of this organism, which has now come to be classed as Cryptococcus neoformans but is also known as Cryptococcus hominis and Torula histolytica was first isolated and described in 1894 by Busse. Sanfelice at the same time isolated a yeast from peaches, to which he gave the species term of neoformans. The first human case of torulosis of the nervous system properly diagnosed was reported by Versé in 1914. Two years later, Stoddard and Cutler reported 2 cases naming the organism Torula histolytica because of what they thought to be a histolytic action of the organism in producing cysts in the tissue. Apparently, there are many strains of pathogenic cryptococci, possibly twenty-two in all, of varying pathogenicity but biologically similar.

Although considered a rare disease, torulosis is the most frequent cause of mycotic meningitis in man. There is an increasing importance of mycotic disease in the United States; the total deaths attributed to this group was greater in each year from 1949 through 1952 than the combined fatalities caused by Rickettsia, protozoal and helminthic diseases. Notwithstanding this increase in incidence, it is believed that many cases go unrecognized. Many cryptococcal infections are diagnosed only post mortem and based on the small percentage of cases in which autopsy is performed, the actual incidence of cryptococcosis must be much higher than that conveyed by the medical literature.2

Clinically, cryptococcosis of the central nervous system may manifest itself in a variety of ways. Some of the diagnoses that have been made, and patients treated for, were: spinal cord tumor, brain abscess, general paresis, brain tumor, encephalitis and more particularly tuberculous meningo-encephalitis. In the case reported here

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* Appreciation is expressed to Gavin Hildick-Smith, Associate Medical Director of The Squibb Institute for supplying the Amphotericin B.
the patient had previously, on two hospital admissions, been worked-up and treated as having a brain tumor. In a review of the literature by Carton and Mount in 1951, it was revealed that there were 42 cases in which neurosurgical procedures were performed, with a total of 62 operations. There were 24 exploratory operations: 12 supratentorial, 9 infratentorial, and 3 laminectomies. In addition to this there were 11 decompressive procedures. Localized cryptococcal granulomata may occur and become of sufficient size that they require attention as a mass lesion. The diffuse cryptococcal leptomeningitis may also produce a picture of an expanding, intracranial lesion. In the report cited there was no mention of a case in which there had been an obstruction of the aqueductus Sylvius and a Torkildsen's procedure performed.

**CASE REPORT**

*B.G.-001 408.* A 46-year-old white male was admitted to the Eugene Talmadge Memorial Hospital on Nov. 1, 1956, at which time he was stuporous and had a left hemiplegia. In April 1954 he had been admitted to another hospital because of nausea and vomiting, visual and auditory hallucinations, unsteadiness on his feet, and nuchal rigidity. Diagnostic studies performed at that time included a pneumoencephalogram and it was thought he had a tumor of the right parietal lobe. Biopsies were taken which were reported to have shown evidence of a malignant brain tumor. The patient had a subtemporal decompression performed on the right and the family was advised he had a malignant tumor and that nothing more could be done. He apparently showed an improvement in his mental state for a matter of several months but began to have severe headaches, progressive weakness of the left lower extremity, nausea and vomiting, and a cloudy sensorium. It was noted by the family that the subtemporal decompression bulged. He was admitted to another hospital where the site of decompression was pulseless, tense and firm. He was responsive only to deep and painful stimuli. An exploratory trephine was placed in search of tumor. The following day he was transferred to our hospital.

**Examination.** Blood pressure was 160/100, respiratory rate 18, pulse rate 78, and temperature 36.8°C.

Scars of the previous trephinations in the frontal region were on each side of the sagittal suture and there was another old scar, 8 cm. long, perpendicular to the right zygomatic process. This was over the site of the bulging temporal decompression. There was a fresh wound and trephine opening over the right parietal area. The brain was tense, prominent and non-pulsile. Pupils were dilated but did react. There was nuchal rigidity with stiffness and pain on motion.

Roentgenograms of the skull revealed stippled calcification in the region of the dorsum sellae and erosion of the posterior clinoid processes. Right carotid arteriography revealed evidence of internal hydrocephalus. Ventriculography performed through the previously placed trephine revealed a complete block between the 3rd and 4th ventricles; 10 cc. of phenolsulfonphthalein instilled in the right lateral ventricle failed to be recovered in the lumbar subarachnoid space. With a ventricular needle in place, air was placed in the lumbar subarachnoid space and this ascended to fill the 4th ventricle and the great cistern, which did not seem to be displaced or of unusual configuration. It was felt that the patient had an internal hydrocephalus caused by aqueductal block.

**Operation.** A Torkildsen procedure was performed, with immediate improvement in the patient's sensorium.

The spinal fluid, examined by Dr. Shepherd of the Clinical Laboratory, Department of Pathology, Medical College of Georgia, revealed *Cryptococcus neoformans*, both encapsulated and non-encapsulated. The count of organisms was extremely heavy. Culture showed an extensive growth. Spinal fluid glucose was 78 mg. per cent; chlorides were 180 mEq.; colloidal gold curve read 555442100; Pandy was reported as 4 plus, and there were 11 white blood cells, with 6 polymorphonuclear leucocytes and lymphocytes.
Course. The patient was immediately started on tetracycline, nystatin, Ethyl Vanillate, and sodium bicarbonate. In spite of this medication the patient continued to run a downhill course and appeared moribund. Repeated studies of the spinal fluid showed increasing counts of organisms and positive cultures. On Dec. 6, 1956, the patient was started on Amphotericin B, 50 mg. I.V. daily; 2 days later he began to show improvement. He received a total of 2 gm. of Amphotericin B over a period of 40 days at 50 mg. daily. The Amphotericin B was stopped on Jan. 18, 1957. A lumbar puncture on Jan. 19, 1957 revealed no evidence of Cryptococcus neoformans. The cultures were negative. The spinal fluid smear was negative. The patient was discharged on Jan. 22, 1957.

He was seen again as an out-patient on Feb. 13, 1957. The site of the decompression was flat and pulsile. The patient showed steady improvement in strength and was completely ambulatory, although he had tremors of both arms and an involuntary tremor. He had no headache, his sensorium was perfectly clear and he had been doing odd jobs about the home. He was admitted for 24 hours for a lumbar puncture. His opening pressure was 100 mm. of water with a negative Queckenstedt response. The fluid was slightly xanthochromic but clear. A smear of the spinal fluid showed no evidence of organisms, and cultures of the spinal fluid were negative. Urinalysis was normal. Nonprotein nitrogen was 38 mg. per cent. Fasting blood sugar was 102 mg. per cent. Hemoglobin was 16.4 gm. and hematocrit 46. Count of white blood cells was 8,250, with 50 per cent segmenters, 34 per cent lymphocytes, 10 per cent monocytes, 5 bands and 1 eosinophil. The platelets appeared normal. The red blood cells were normal. Prothrombin time was 100 per cent at 12.5 sec. Spinal fluid sugar was 68 mg. per cent, chloride 11 mg. per cent, protein 350 mg. per cent, Pandy 3 plus, and there were 32 cells/cc.

The patient was seen again on Feb. 27, 1957. His course had been one of progressive improvement. He continued to show a slight involuntary tremor of the extended extremity on the left. There had been improvement in the tremor in the right upper extremity. The gait showed slight incoordination, mainly in the left extremity. Reflexes were hyperactive on the left.

On March 27, 1957 his general condition was improved. He had gained 23 lbs. since his discharge. Neurological findings were essentially as seen on Feb. 27, 1957. There were still hyperactive reflexes and slight tremor on the left. The site of the right temporal craniotomy was flat and pulsile, and there was no evidence of any active disease. The patient had been maintained on Dilantin 100 mg. b.i.d. and Phenobarbital 100 mg. at bedtime. He was receiving no other medication.

He was seen again in April 1957. At this time he drove his automobile to the clinic. He had returned to doing his work on a small farm and he was asymptomatic. A lumbar puncture performed at this time showed no organisms and there was no evidence of growth on Sabouraud's culture after 10 weeks' incubation at 27°C.

Since this report was submitted for publication, the patient was seen again in June 1958. He continues to remain well and is carrying on his duties on a farm. The cerebrospinal fluid remains normal.

**DISCUSSION**

Amphotericin B, an antibiotic formed by a species of Streptomyces isolated from soil obtained from South America has been shown in vitro, and in animals in vivo, to inhibit the growth of Cryptococcus neoformans.

The chemical structure of Amphotericin B is not known. It is a relatively stable antibiotic, even at temperatures as high as 40°C. Absorption from the gastrointestinal tract appears to be minimal. By the intravenous route the bioactivity of the blood plasma is maintained high for several hours. The drug is quickly adsorbed to the red blood cells and the maximum excretion by the kidneys occurs during the first 3 hours. Amphotericin B appears to be antifungal not only against Cryptococcus neoformans, as shown in vitro, but also against other yeast and yeast-like
fungi, including Candida albicans, Blastomyces dermatitidis, Blastomyces brasiliensis, Sporothrix schenckii, and Histoplasma capsulatum. Animal in vivo studies show it to be effective not only in Cryptococcus neoformans, but also in Candida albicans, Coccidioides immitis, Histoplasma capsulatum and Trichophyton mentagrophytes.

The mode of action of Amphotericin B is fungicidal and Mycostatin appears to have an additive or synergistic effect. Amphotericin B appears to have little or no antibacterial activity.

Administration. Amphotericin B is formulated as a freshly prepared sterile suspension and is administered by mixing 50 mg. in 50 cc. sterile 5 per cent glucose in water. Effort must be made to have all of the suspension agitated into solution before administration by slow intravenous drip over a period of approximately 5-6 hours. Mild febrile reactions may be observed during and after the administration. If a febrile reaction occurs during administration, therapy is halted until this reaction is over. Phlebitis at the site of injection may be seen, but usually this will not occur if the rate of injection is sufficiently slow. Frequent inspection of the dripping suspension should be made to avoid the administration of precipitated material; this can be prevented by repeated agitation.

This patient presented a very confusing problem. He had been originally operated upon and advised that he had a malignant glioma of the brain. He had shown a temporary improvement following the subtemporal decompression and biopsy in April 1954 only to have a recurrence of his headache, nuchal rigidity, and clouding of his sensorium. He was seen again in October 1956 because of a progressive downhill course at which time the skull was trephined and exploration with a needle was performed in an attempt to hit a tumor cyst or to localize a mass lesion. He then was admitted to our hospital for evaluation and treatment.

It was postulated that his left hemiplegia was the result of increased intracranial pressure secondary to the internal hydrocephalus, which forced the right motor strip tight against the bony edge of the decompression craniectomy of the right temporal and parietal bones, making this a paralysis secondary to pressure alone and not caused by a localized encephalitis. This hypothesis was borne out by the fact that the hemiparesis showed immediate improvement after decompression of the lateral ventricles with the Torkildsen procedure. Although this patient had received the various drugs mentioned, namely; mystatin, Ethyl Vanillate, tetracycline and alkalinization by excessive doses of sodium bicarbonate, his course continued downhill. The use of these other drugs could well serve as a control in this individual, inasmuch as the spinal fluid showed increased cell count and growth and the clinical condition of the patient worsened daily, until the addition of Amphotericin B, when he began to improve.

ADDENDUM

Since submitting this report, a second patient with Torula meningo-encephalitis has been treated with Amphotericin B. The cerebrospinal fluid became free of organisms during treatment and has remained so for 7 months. The patient is well clinically and has resumed his usual activities.

REFERENCES