Canad. Med. Ass. J.
Sept. 14, 1968, vol. 99

CASE REPORTS

Listeria Meningitis

M. NEWMAN, M.D. and D. NORRIS, M.Sc., *Winnipeg, Man.*

ALTHOUGH *Listeria monocytogenes* is widespread as a pathogen among domestic animals, human infections are uncommon and their occurrence is usually unrelated to occupation or association with sick animals. Following the discovery of this organism in 1926 by Murray, Webb and Swann,[1] it was many years before more than an occasional human case was reported in the literature. In the last 20 years, however, numerous cases in infants and adults have been reported in Europe and North America. Seeliger[2] has described all the principal clinical forms of the disease in man.

The following case report is presented because it indicates the importance of early recognition of the condition and the institution of proper treatment.

A 67-year-old woman who had been found in a state of collapse at home was brought to hospital by the police. She was unable to give any history, but she had been seen around her home two days before, apparently in good health.

On examination at 9:30 a.m. on May 18, 1967, she would not speak to or co-operate with the examiner. Her temperature was 101° F., and her pulse was 100 per minute. There was evidence that she had diarrhea. By 4:30 p.m. her condition had deteriorated. She was unresponsive when addressed and irritable when examination was attempted. She withdrew vigorously from all stimuli. She could move all four limbs but she did not speak. Neck rigidity and Kernig's sign were present. No abnormality of cranial nerve function was detected, nor was there any paralysis or spasticity. Tendon reflexes were very brisk and symmetrical, and the plantar responses were flexor. Physical examination of her chest, heart and abdomen was normal. There was no discharge from her nose, pharynx or ears. The blood pressure was 156/80 mm. Hg.

A lumbar puncture at 4:30 p.m. yielded cloudy fluid containing 391 white cells per c.mm. of which 75% were neutrophils; the protein content was 152 mg. per 100 ml., and glucose less than 10 mg. per 100 ml. A smear of the spinal fluid stained by Gram's method revealed only an occasional gram-negative coccobacillus which resembled hemophilus, but the size of the organism left some doubt about this possibility.

Examination of the blood showed: hemoglobin 12.1 g. per 100 ml.; leukocyte count 18,400 per c.mm. of which 91% were neutrophils; urea nitrogen 15 mg. per 100 ml.; serum sodium 124 mEq. per litre; serum potassium 3.4 mEq. per litre. The blood culture showed no growth of organisms. Culture of swabs from the throat and nose grew *Staphylococcus albus*, non-pathogenic Neisseria and diphtheroids. Culture of stool specimens grew *E. coli* and fecal streptococci. Urinalysis showed no sugar and no pus cells, but the protein content was 100 mg. per 100 ml.

The electrocardiogram showed left ventricular predominance. Chest radiographs showed enlargement of the left ventricle, emphysema of the lungs, and inflammation of the right middle lobe.

Treatment was started with 5 million units of penicillin and 1 g. chloramphenicol in an intravenous drip. After the initial examination of the spinal fluid smear at 6 p.m., the therapy was changed on the presumption that a hemophilus infection would be proved. Ampicillin 1 g. every eight hours in an intravenous drip was given in place of penicillin, and chloramphenicol was continued 0.5 g. every eight hours. On the following day, May 19, the patient was less reactive to stimuli, and on May 20 her temperature was still 103° F. and she responded only to very painful stimuli. By this time the organism in the cerebrospinal fluid was identified as *Listeria monocytogenes* and a preliminary sensitivity determination showed resistance to ampicillin but sensitivity to streptomycin, chloramphenicol, erythromycin and tetracycline. Ampicillin was therefore stopped and chloramphenicol was continued, with the addition of streptomycin 1 g. intramuscularly every eight hours.

Over the next two days her temperature returned to normal, but she did not regain consciousness. The level of serum sodium fell to 120 mEq. per litre and the white cell count fell to 5400 per c.mm. with 84% neutrophils. She was treated with normal saline infusion and on May 27 feeding by gastric tube was begun. On this day, lumbar puncture was repeated and the fluid was found to contain 95 white cells per c.mm., of which 75% were neutrophils; protein 152 mg. per 100 ml., and glucose 63 mg. per 100 ml. A smear of centrifuged spinal fluid revealed a moderate number of ghost cells and some irregularly staining bacilli. On this occasion culture of the spinal fluid was negative.

From St. Boniface Hospital, Manitoba.
Reprint requests to: Dr. M. Newman, St. Boniface Hospital, St. Boniface, Manitoba.

On May 30, chloramphenicol was stopped and intravenous pyrrolidinomethyl tetracycline (Reverin) 275 mg. every eight hours was started. Streptomycin 0.5 g. twice daily was continued until June 8; the intravenous tetracycline was stopped on June 5.

On June 6 the spinal fluid revealed 7 white cells per c.mm.; protein 40 mg. per 100 ml.; and no bacteria on smear or culture. On June 9 the levels of serum electrolytes were much improved—sodium 130, potassium 3.3 and chloride 86 mEq. per litre—and she was responding once more to objects moving in front of her eyes. She could open and close her eyes and mouth and move all four limbs. Twitching movements of the upper limbs were observed. She did not respond to verbal commands and she did not speak. By June 12, she had improved further and was able to lift her right hand and put out her tongue when asked, but she could not lift her left hand. She had a severe ataxic dysarthria and a severe ataxia with intention tremor of both arms and legs, but no nystagmus. She was now able to feed herself. Radiographs of her chest had become normal again. Four months later, in October 1967, she was alert and responded normally to people and to speech. Her balance was still very poor, but she was able to stand with the assistance of one person. She could feed herself. Her speech was dysarthric, but with patience it could be understood.

DISCUSSION

Listeria monocytogenes is morphologically a diphasic organism. In the smooth phase, there is a predominance of small, gram-positive organisms which measure 0.5 μ by 1 to 2.5 μ and occur singly or in short chains. In the rough phase, long filaments up to 60 μ in length are seen. Old cultures reveal short filaments, rods and few coccal forms.[3] The most deceiving aspect of the morphological appearance of the organism is that it readily loses its gram-positive characteristics and appears gram-negative. It is this feature, coupled with its morphological resemblance to the hemophilus group, that challenges the bacteriologist.

The appearance of the colonies also gives little help in the recognition of this organism. It grows slowly, and on blood agar the colonies resemble those of a diphtheroid or a streptococcus; when smears are made from these colonies and stained by Gram's method, the organism may resemble a diphtheroid and be considered as a contaminant. Any isolate showing these characteristics must be examined closely for Listeria. The quickest way to confirm the possibility is to check the ability of the organism to exhibit growth and motility at both room and refrigerator temperature in a motility test medium. Diphtheroids are non-motile, and Listeria exhibit a characteristic tumbling motion. If motility is noted, further tests must be performed. Bergey's "Manual of Determinative Bacteriology" will guide the examiner to the tests required for final identification.

The organism is generally sensitive *in vitro* to streptomycin, chloramphenicol, erythromycin and the tetracyclines, and partly sensitive to penicillin and the sulfonamides. Seeliger has collected the results of therapy in 44 adults with listeriosis of the central nervous system. Of 20 patients treated with tetracycline, 17 recovered and 3 died. Of 24 patients treated with antibiotics other than tetracycline, 13 recovered and 11 died. Seeliger concludes that in spite of the *in vitro* sensitivity of the organism to other antibiotics, the tetracyclines are superior in the treatment of listeriosis. Resistance to streptomycin develops rapidly; some strains are resistant to chloramphenicol; and very few clinical successes have been reported with penicillin. Dedrick[4] draws similar conclusions from a slightly smaller series treated in the United States. Macnair, White and Graham[5] advocate ampicillin, but our patient definitely did not respond to this drug.

Therefore, although penicillin, ampicillin and chloramphenicol are the mainstays of treatment in pyogenic meningitis when the cause has not yet been ascertained, tetracycline is the drug of choice as soon as Listeria infection is suspected. In this patient, penicillin, ampicillin and chloramphenicol failed to control the infection, whereas tetracycline was undoubtedly effective. It would seem reasonable to give the maximum dose by the quickest route, and for this reason intravenous pyrrolidinomethyl tetracycline (Reverin) is recommended.

Some infections with *Listeria monocytogenes* may be subclinical or self-limiting, but involvement of the central nervous system is fatal unless adequate treatment is given. If effective treatment is delayed, as it was in this case, permanent disability from involvement of the brain stem may occur. Early bacteriological diagnosis is vital.

REFERENCES

1. MURRAY, E. G. D., WEBB, R. A. AND SWANN, M. B. R.: *J. Path. Bact.*, **29**: 407, 1926.
2. SEELIGER, H. P. R.: Listeriosis, foreword by K. F. Meyer with an introduction to the 2nd German edition by H. Eyer, Hafner Publishing Company Inc., New York, 1961.
3. DUBOS, R. J. editor: Bacterial and mycotic infections in man, 2nd ed., J. B. Lippincott Co., Philadelphia, 1952, p. 501.
4. DEDRICK, J. W.: *Amer. J. Med. Sci.*, **233**: 617, 1957.
5. MACNAIR, D. R., WHITE, J. E. AND GRAHAM, J. M.: *Lancet*, **1**: 16, 1968.