İnfeksiyon Dergisi (Turkish Journal of Infection) 2003; 17 (3): 341-343

LISTERIA MONOCYTOGENES MENINGITIS: AN ADULT CASE SUCCESSFULLY TREATED WITH THE COMBINATION OF RIFAMPIN AND AMPICILLIN

LISTERIA MONOCYTOGENES MENİNJİTİ: AMPİSİLİN VE RİFAMPİN KOMBİNASYONUYLA TEDAVİ EDİLEN ERİŞKİN BİR OLGU

S. Sırrı KILIÇ[1] İlhami ÇELIK[1] Ahmet KALKAN[1] Ali Osman KILIÇ[2]

[1] Department of Clinical Microbiology and Infectious Diseases, Faculty of Medicine, Fırat University, Elazığ
[2] Department of Oral Biology, College of Dentistry, University of Illinois, Chicago, USA

Key Words: *Listeria monocytogenes*, meningitis, rifampin, ampicillin, treatment
Anahtar Sözcükler: *Listeria monocytogenes*, meninjit, rifampin, ampisillin, sağaltım

SUMMARY

A case of meningitis due to Listeria monocytogenes is presented. The patient, a 60-year-old male, receiving the prediagnosis of acute bacterial meningitis, was first treated with ceftriaxone. Upon progression of clinical findings and consideration of his family history of tuberculosis and the compatibility of cerebrospinal fluid (CSF) findings with tuberculous meningitis, anti-tuberculous treatment was implemented. An agent was isolated in his cerebrospinal fluid 24 hours after the implementation of anti-tuberculosis treatment. The agent was identified as L. monocytogenes. All of the anti-tuberculosis drugs were stopped except rifampin to which ampicillin was added. The case was cured with the combination of ampicillin and rifampin.

ÖZET

Listeria monocytogenes meninjitli bir olgu sunulmuştur. Akut bakteri meninjiti öntanısıyla seftriakson tedavisi başlanan 60 yaşındaki erkek hastaya, klinik bulgularının tedaviye karşın gittikçe kötüleşmesi, soy geçmişinde tüberküloz öyküsü olması ve beyin-omurilik sıvısı (BOS) bulgularının tüberküloz meninjitle uyumlu olması üzerine dörtlü anti-tüberkülo başlandı. Anti-tüberkülo tedaviye başlandıktan 24 saat sonra BOS kültüründe L. monocytogenes üredi. Rifampin dışındaki diğer antitüberkülo ilaçlar kesildi ve tedaviye ampisilin eklendi. Olgu rifampin-ampisilin kombinasyonu ile iyileşti.

INTRODUCTION

There have been no controlled clinical trials to establish a drug of choice for listerial infection, but ampicillin is generally considered as the agent of choice. Most authorities suggest adding gentamicin to ampicillin for treatment of severe listerial infections such as bacteremia, central nervous system infection and endocarditis (1-3). Nevertheless, these drugs are bacteriostatic for listeriae. Rifampin could be consired an alternative drug to obtain a bactericidal effect and to be used in combination with ampicillin (2-5).

In this paper, a case of listerial meningitis is presented. This case was treated with the combination of ampicillin and rifampin. The diagnosis and treatment of the infection were discussed in the light of available literature.

CASE

A 60-year-old male farmer, previously healthy, but complaining of sudden onsets of severe headache, nausea, vomiting and fever had been diagnosed as acute bacterial meningitis after a six-hour examination by a specialist of infectious diseases and the empirical

treatment had begun with intravenous ceftriaxone and methyl prednisolone for four days. On the first day of the therapy, the patient had become conscious. After the second day, however, he had become unconscious again and agitated. Other serious general health symptoms occurred on the fourth day, and then patient was sent to the hospital. He was agitated, uncooperative, unoriented and unconscious when he was admitted to the clinic. Arterial blood pressure of the patient was 190/100 mm Hg, heart rate, 100/minute; ventilation, 24/minute, and the body temperature was 39° C. As to meningeal irritation findings; nuchal rigidity, Kernig's and Brudzinski's signs were present, but no neurological disorders were determined. He was in moderate coma according to the Glasgow Coma Score (8/15).

Leukocyte count was 8.700/mm^3 (78% neutrophils, 10% lymphocytes, 12% monocytes); platelet count, 129.000/mm^3; erythrocyte sedimentation rate (ESR), 27 mm/hour; and C-reactive protein (CRP) 14 mg/dL. The values of AST (80 U/L), ALT (54 U/L), LDH (864 U/L), urea (58 mg/dL), creatine (1.1 mg/dL) and other biochemical parameters were in normal ranges. The cerebrospinal fluid (CSF) was xantochromic with an opening pressure of 300 mm H_2O, and the analysis of CSF showed the following: leukocyte count 450/mm^3 (70% mononuclear, 30% polymorphonuclears). The level of CSF glucose was 8 mg/dL (simultaneously blood glucose: 170 mg/dL); protein, 350 mg/dL; chloride, 112 mmol/dL; sodium, 145 mmol/dL. No microorganism was determined in CSF with the Gram and Ehrlich Ziehl-Neelsen stains. Cranial magnetic resonance imaging showed deepening of cerebellar folia, cerebral sulcus in supratentorial space, deepening in the cisterns and a minimal significance in lateral ventricle as well as diffuse cerebral edema.

Since the patient was unconscious, proper cooperation with the patient was not possible, but his relatives provided a history of tuberculosis in his youth. However, no clear information about any treatment of this past illness was evident. Additionally, it was learned that his brother had been receiving treatment for lung tuberculosis. There was linear density increase in the right upper zone at chest x-ray. No response was obtained with empirical ceftriaxone therapy. Upon the prediagnosis of tuberculous meningitis, a combination of four antituberculosis regimen was started: (Isoniazid (INH) 300 mg, rifampin (RFM) 600 mg, streptomycin (STR) 1 g, pyrazinamide (PZA) 3 g and 8 mg dexamethasone at every 6 hours. Twenty-four hours after the initiation of anti-tuberculous treatment, a CSF culture on blood showed narrow beta-haemolysis zone forming, dark-white colored fine surfaced colonies which were then identified as *Listeria monocytogenes*. The diagnosis was confirmed by polymerase chain reaction by 16 S rRNA gene sequence, using universal primers. With antibiotic susceptibility test using disk diffusion according to the guidelines of NCCLS, the agent was found susceptible to ampicillin, vancomycin, rifampin, gentamicin, chloramphenicol and penicillin G, but resistant to ceftriaxone.

On the second day of anti-tuberculosis therapy, the patient was still in a mid-level coma. After obtaining antibiotic susceptibility test results on the third day, ampicillin (four gram injections at every eight hour) was begun; and INH, STR and PZA were removed from the treatment. Rifampin and dexamethasone administration were continued. After the fourth day of the anti-tuberculosis treatment, the patient was afebrile and conscious and as his general symptoms improved. Dexamethasone administration was stopped on day 10 while ampicillin and rifampin were continued for 21 days. After the treatment, CSF cell count and biochemical parameters returned to normal levels and the patient recovered without sequelae.

DISCUSSION

Ampicillin is the most active agent in the treatment of *L. monocytogenes* meningitis while third generation cephalosporins are found ineffective in the treatment (1, 2). Results from *in vitro* studies have indicated that antibiotics such as chloramphenicol, erythromycin, doxycyclin, rifampin, and trimethoprim-sulfamethoxazole are also effective in this clinical entity. Clinical studies on the therapy of the infection show the efficacy of the mentioned antibiotics except penicillin derivatives and trimethoprim-sulfamethoxazole (3-8). Unfortunately, most antibiotics are not bactericidal for *Listeria*. Drug combinations may exert a synergistic effect. Furthermore, the efficacy of therapy is limited by intracellular habitat of pathogenic listeriae (1-6). The clinical experience is that the combination of amoxicillin and gentamicin is still the best opinion (1, 2). Despite the effectiveness of the antibiotics in *in vitro* studies, clinical studies have shown that rifampin administration alone is not effective. *In vitro* studies on the clinical isolates reported a rare additive effect with rifampin-ampicillin combination, but generally, antagonistic effect was obtained (3-8). On the other hand, there are *in vitro* studies reporting synergistic effect obtained with combined use of rifampin and ampicillin. Rifampin also has a good penetration into phagocytic cells. It is suggested that further clinical studies are needed for this combination (2-7).

In the present case, on the third day of anti-tuberculosis treatment, all the antituberculous drugs were stopped except rifampin to which dexamethasone and ampicillin were added. After the fourth day, the fever felldown to

normal, patient regained consciousnors and his general symptoms improved. This recovery might have been dependent on the effect of rifampin. Steroids might have also contributed to the improvement of clinical symptoms. No improvement was observed with the initial empirical treatment that included neither prednisolone, and clinical improvement achieved on the fourth day cannot be due to dexamethasone. The combination of ampicillin and rifampin was administered for 21 days. Clinical findings and CSF parameters of the patient were completely normal at the end of the treatment. The administration of this drug combination indicated the absence of antagonistic effect in *in vivo*.

In conclusion, *L. monocytogenes* should also be considered as an agent when etiological diagnosis of meningitis is to be made. This case is presented to emphasize the negative outcome of empirical treatment when *L. monocytogenes* was not considered. Additionally, the administration of a rifampin and ampicillin combination for treatment should be further studied in future investigations.

REFERENCES

1. **Lorber B.** *Listeria monocytogenes. In:* Mandell GL, Douglas R, Bennett JE, eds. *Principles and Practice of Infectious Diseases.* 5th ed. New York Churchill Livingstone, **2000:** 2208-15.
2. **Lorber B.** Listeriosis. *Clin Infect Dis* **1997;** 24: 1-11.
3. **Vela AI, Fernandez-Gayayzabal JF, Latre MV, Rodruguez AA, Dominiguez AA, Moreno MA.** Antimicrobial susceptibility of *Listeria monocytogenes* isolated from meningoencephalitis in sheep. *Int J Antimicrob Agents* **2001;** 17: 215-20.
4. **Boisivion A, Guiomar C, Carbon C.** *In vitro* bactericidal activity of amoxicillin, gentamicin, rifampicin, ciprofloxacin and trimethoprim-sulfamethaxazole alone or in combination against *Listeria monocytogenes. Eur J Clin Microbiol Infect Dis* **1990;** 9: 206-9.
5. **Scheld WM.** Evaluation of rifampin and other antibiotics against *Listeria monocytogenes in vitro* and *in vivo*. *Rev Infect Dis* **1983;** 5: 593-9.
6. **Marco F, Almela M, Nolla-Salas J, et al.** *In vitro* activities of 22 antimicrobial agents against *Listeria monocytogenes* strains isolated in Barcelona, Spain. The Collaborative Study Group of Listeriosis of Barcelona. *Diagn Microbiol Infect Dis* **2000;** 38: 259-61.
7. **Michelet C, Avril JL, Arvieux C, Jacqulinet C, Vu N, Cartier F.** Comparative activities of new fluoroquinolones, alone or in combination with amoxicillin, trimethoprim-sulfamethaxazole, or rifampin, against intracellular *Listeria monocytogenes. Antimicrob agents Chemother* **1997;** 41: 60-5.
8. **Tuazon CU, Shamsuddin D, Miller H.** Antibiotic susceptibility and synergy of clinical isolates of *Listeria monocytogenes*. *Antimicrob Agents Chemother* **1982;** 21: 525-7.