SUCCESSFUL THERAPY OF POSTNEUROSURGICAL MENINGITIS CAUSED BY A RESISTANT STRAIN OF ENTEROBACTER AEROGENES

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Introduction

Gram-negative bacillary meningitis (GNBM) is commonly seen in infants and neonates. However, GNBM can cause severe meningitis in adults, although rarely.\cite{1,2} It usually occurs after central nervous system trauma and neurosurgical procedures. The immunocompromised, the elderly, or patients with chronic diseases are at high risk.\cite{1,3} Numerous antibiotics have been tried in the treatment of GNBM, but overall, the therapeutic results have been largely unsatisfactory, and mortality as high as 70% has been reported.\cite{4}

We present a patient who was successfully treated with trimethoprim-sulfamethoxazole (TMP-SMX) and gentamicin with Enterobacter aerogenes meningitis following neurosurgery. Recent literature has focused on the successful treatment of GNBM with newer agents such as third generation cephalosporins and aztreonam. However, with increasing resistance of Gram-negative bacteria to beta-lactam antibiotics, alternative regimens need consideration based on the individual institution’s antibiogram, as our case illustrates.

Case Report

A 39-year-old man presented with an 11-month history of progressive visual loss and headaches. Computed tomography of the head revealed a 7 x 8-cm frontal-sella turcica mass invading the maxillary, ethmoid, and sphenoid sinuses (Fig 1). Physical examination demonstrated exophthalmos and bilateral diminished vision.

The arterial supply of the mass was embolized. The tumor was resected via bifrontal craniotomy and was a meningioma. Prophylactic clindamycin and nafcillin were administered postoperatively. Six days following the operation, he developed a fever of 105 degrees Fahrenheit with agitation, lethargy, and combativeness. A cerebral spinal fluid leak with rhinorrhea was noted.

Cerebral spinal fluid (CSF) obtained by a lumbar puncture revealed glucose of 20 mg/dL, protein of 222 mg/dL, and a white blood cell count of 3100/cu.mm. The Gram stain showed 2+ white blood cell count but no organisms. CSF cultures grew E aerogenes with two different morphologies of colony growth (Fig 2). Organisms from one of the colony types were susceptible to all antibiotics tested, and the other was resistant to ceftazidime and piperacillin but sensitive to ciprofloxacin, TMP-SMX, and aminoglycosides by the automated Vitek system. TMP-SMX was substituted for ceftazidime, and gentamicin was added.

The patient’s fever resolved promptly, and his mental status improved. Repeat CSF analysis demonstrated protein of 221 mg/dL, glucose of 38 mg/dL, and a white blood cell count of 990/cu.mm with 91% neutrophils, and a red blood cell count of 50/cu.mm. The CSF cultures were negative. Additional CSF analyses at one and four weeks later remained sterile. After 21 days of intravenous administration of TMP-SMX followed by 14 days of oral TMP-SMX, the patient remained asymptomatic.

The CSF leak required placement of a lumbar drain. However, the leak recurred after removal of the drain, and a ventriculo-peritoneal (V-P) shunt was placed with resolution of the leak. Since the placement of the V-P shunt, all subsequent CSF analyses have been negative for any infection. After six months, the patient had no sensory or motor deficits but remained legally blind.
Meningitis caused by Gram-negative enteric bacteria is rare in adults but can be found most often after disruption of the dura-arachnoid barrier secondary to trauma or neurosurgery. It may also occur spontaneously in patients who are elderly, immunocompromised, or chronically debilitated. It occasionally spreads directly from an adjacent focus of infection as in the case of mastoiditis or sinusitis. The most common organisms involved are Klebsiella sp, Pseudomonas sp, Escherichia coli, and Haemophilus influenzae. Enterobacter sp are rarely the causative agents.

Over the last decade, the choice of antibiotics for GNBM has varied greatly. Overall unsatisfactory results and mortality rates as high as 70% have been reported. For years, chloramphenicol was the standard therapy for GNBM. Chloramphenicol offered not only in vitro inhibitory activity against most of the offending organisms except Pseudomonas aeruginosa, but also the ability to enter the CSF when given intravenously. However, its action against aerobic Gram-negative organisms is only bacteriostatic at levels obtainable in the CSF. In vivo resistance during therapy can occur, and antagonism when used in combination with gentamicin or cefotaxime has been reported. Aminoglycosides, which have been frequently used, are associated with low systemic therapeutic-toxic ratio, diminished effectiveness in actively infected CSF, and difficulty in obtaining bactericidal levels in the CSF. The third generation cephalosporins, including moxalactam, ceftriaxone, cefotaxime, and ceftazidime are effective against GNBM and enter the CSF in high bactericidal concentrations.

Treatment failures have been reported, and several agents in this group have been associated with hyponprothrombinemia and platelet dysfunction with increased risk of hemorrhage. Aztreonam, which covers a broad range of Gram-negative bacteria, has been shown to reach therapeutic levels in the CSF regardless of inflamed or noninflamed meninges. Investigators have documented high microbiologic cure rates with aztreonam, so it must be regarded as one of the front-line agents in the treatment of GNBM.

The combination of TMP-SMX, which became available for intravenous use in the mid 1970s, has long been known to be active against many Gram-negative bacilli. It quickly enters the CSF to establish bactericidal levels. The use of TMP-SMX to treat GNBM in neonates and infants was reported in 1969, followed by later reports of TMP-SMX use in the treatment of a bacterial brain abscess with documentation of bactericidal levels in the abscess cavity, and the successful treatment of five patients with meningitis. In 1982, successful treatment of a patient with Klebsiella pneumoniae meningitis using TMP-SMX was reported. In a worldwide review of the literature in 1984 for cases of meningitis treated with TMP-SMX, Levitz and Quintiliani obtained data on 33 patients with GNBM treated with TMP-SMX. Seventeen of the cases were from published reports, and 16 were unpublished cases reported to pharmaceutical companies. Bacteriologic cure was achieved in 26 of the 33 patients. In two of these cases, the causative agent was Enterobacter cloacae, which generally is only moderately sensitive to third-generation cephalosporins. Treatment with TMP-SMX in both patients resulted in clinical and bacteriologic cure. A similar successful outcome using TMP-SMX was obtained in a postoperative patient with E cloacae meningitis. The organism demonstrated both an inducible beta-lactamase and a constitutive beta-lactamase that resulted in a poor response to cephalosporin therapy.

Clinical trials have not yet been performed to determine the value of TMP-SMX in the treatment of GNBM. However, Wolff et al. reported a 100% (5/5) cure rate of Enterobacter sp menigitis with TMP-SMX alone. Faced with a multiple drug resistance strain of E aerogenes, we chose to treat the patient with TMP-SMX and gentamicin intravenously with a successful outcome. Despite the recognition that intrathecal gentamicin is necessary to obtain bactericidal levels in CSF, we used intravenous gentamicin for synergy with TMP-SMX in serum and possibly in CSF. Imipenem/cilastatin and ciprofloxacin are alternatives to treat Gram-negative bacterial meningitis. However, the risk of seizures and mental status changes with the former and poor CSF penetration (10% of peak serum concentration) with the latter make these options less desirable. Meropenem, a new carbapenem, has been used successfully to treat resistant pseudomonas aeruginosa meningitis and probably would be effective against enterobacter with less risk of seizures.

We agree with previous reports that in a select group of patients with GNBM with multiple-drug resistance and in vitro susceptibility to TMP-SMX and aminoglycosides, this combination should be considered as a viable and potentially successful treatment option.

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References