Community-acquired *Escherichia coli* meningitis in a diabetic patient

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Gram negative bacilli are a common cause of community acquired bacterial meningitis in neonates and infants but rarely in adults. In the latter, it occurs usually secondary to head trauma or craniotomy.[1] Spontaneous non-traumatic Gram negative bacillus meningitis (GNBM) however, most frequently involves the elderly or those immunosuppressed by a variety of conditions including diabetes mellitus, alcohol induced cirrhosis, malignancies, splenectomy, and steroid therapy.[1] Broad spectrum cephalosporins have been the treatment of choice for GNBM since the late 1980's.[2] There is a notable increase in resistance to these drugs from 1994 onwards, and in one reported series with patients treated over a 12 year period, 9% of GNBM had resistance to third generation cephalosporins.[2] We report a case of ceftriaxone resistant spontaneous *Escherichia coli (E. coli)* meningitis with *E. coli* septicemia in a diabetic patient, who despite a fulminant course, recovered without any disability.

A 47-year-old Yemeni motor vehicle salesman, smoker, teetotal, presented to the emergency department of Riyadh Medical Complex, Riyadh, Kingdom of Saudi Arabia, in a confused and agitated state. History obtained from the relatives revealed that he was apparently well the previous day. He then developed fever with chills, photophobia, and severe dizziness to such an extent that he incurred a scalp injury with laceration of upper occiput, which required 3 stitches at a local dispensary. He then vomited twice, became confused, developed a seizure at home and was brought to hospital, where he vomited 4 times and had another attack of seizure. No history of an ear, nose or throat (ENT) infection was reported. He was diabetic since one year on oral hypoglycemic agents. He had been involved in a road traffic accident 15 years ago with injuries to his left chest wall, which necessitated chest drainage for thoracic empyema and a 2 week admission. He also had a history of malaria 15 years ago, while visiting the southern state of Jeezan. There was no history of any neurosurgical procedures and no history of liver disease or tuberculosis. Clinical examination showed a slenderly built, drowsy, confused and agitated, anicteric male, with clubbed fingers and toes, and poor oral hygiene. His occipital wound was superficial and clean. He was febrile with a temperature of 38.5°C with a regular pulse of 105 beats/min, and blood pressure of 130/90 mm Hg. He had marked neck stiffness with Kerning and Brudzinski sign positive, planter reflexes were downgoing; pupils were normal in size and reactive. No CSF rhinorrhea was noted. Reflexes were normal. Chest examination revealed a linear scar on the lower left chest, along the mid-axillary line, with mild decrease in breath sounds over the same area. Examination of heart, abdomen, and ENT were normal. Urinalysis was unremarkable. His initial complete blood count showed: white blood cells (WBC) of $13x10^3$ with 93% neutrophils, hemoglobin 16.2 g/dl, platelets $204x10^3$. Erythrocyte sedimentation rate was 62mm/1st hour. Blood film for malaria parasite thick and thin twice negative. Blood glucose was 17 mmol/dl with normal kidney function. Liver function test was normal apart from an aspartate level of 53 u/L (normal <31 u/L). Coagulation profile was normal. Lactate dehydrogenase (LDH) was 401 u/l. Hepatitis B and C, as well as human immunodeficiency virus blood screens were negative. Urine cultures showed no growth. Blood and Sputum culture however showed growth of *E. coli*, resistant to ceftriaxone and sensitive to gentamicin and Tazocin, sputum examination was negative for acid fast bacilli (AFB). A Mantoux test was negative. Chest radiograph showed chronic left pleura thickening and calcification, with some volume loss in the left lower lobe. A plain CT of brain was normal. Results of the lumbar puncture (LP) CSF analysis are shown in **Table 1**. He was commenced on treatment with intravenous ceftriaxone 2 grams daily. Gentamicin 80 mgs intravenously every 8 hours was started based on reported cultures and sensitivities. On day 5, he remained febrile and developed right lower motor neuron VII nerve palsy. Repeat plain CT-Brain was normal, LP was repeated. On day 6, he showed some improvement in the conscious level and neck rigidity, and became less febrile, CSF results shown in **Table 1**. The CSF culture sensitivity on day 8 showed the growth of *E. Coli* resistant to ceftriaxone but sensitive to gentamicin, imipenem and Tazocin. The antibiotics were changed to meropenem 2 grams intravenously every 8 hours and gentamicin continued. His CT chest showed left pleural calcification with lower zone minimal basal fibrosis and volume loss. Ultrasound abdomen, serum immunoglobulins, x-ray para-nasal sinuses and CT-temporal bone were all normal. On

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subsequent days he became afebrile, the consciousness level improved remarkably and the meningeal signs disappeared. The results of repeat LP on the 13th day are shown in **Table 1**. The CSF culture and sensitivity report showed no growth on day 18. A repeat blood and sputum culture and sensitivity report showed no growth either. Antibiotics were continued for up to 3 weeks and he was discharged in a good health.

Meningitis due to Gram negative organisms were first recognized and reported in 1892. Among Gram negative bacilli causing meningitis, the most frequently implicated organisms are *E. coli, Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Acinetobacter,* with *E. coli* and Klebsiella accounting for more than 50% of adult cases.[1,2] *Escherichia coli* occurs more often in adults with spontaneous GNBM, like in our case, as well as in nosocomial GNBM complicating neurosurgical procedures, whereas *Klebsiella* is a common cause in the elderly with GNBM.[2] It has been shown that successful traversal of the blood brain barrier (BBB) requires a high degree of *E. coli* bacteremia, invasion of brain microvascular endothelial cells, host cell actin cytoskeleton rearrangements and related signaling pathways, as well as traversal of the BBB as live bacteria.[3] Physical signs of meningitis with altered sensorium, seizures, and neck rigidity are often dramatic in spontaneous GNBM, but subtle when Gram negative infection is associated with skull trauma or neurosurgery.[1] Patients with spontaneous GNBM typically have a more fulminant course with a higher prevalence of bacteremia, shock and death.[1,2] One of the most important factors predicting survival is the state of consciousness at the time of presentation.[1] Patients unresponsive or responsive only to pain had a 49% mortality rate compared to a mortality rate of 16% when they were alert or only lethargic.[1] *Escherichia coli* is the Gram negative bacillus most commonly associated with death.[1,2] Seizures occurring before or sometimes during hospitalization have been predictive of mortality or neurologic sequelae in several studies.[1] Bacteremia is detectable in approximately 50% of adult patients with GNBM, and may precede clinical evidence of central nervous system (CNS) infection. Patients with bacteremia have mortality rates up to 5 times higher than non-bacteremic patients.[1] Since our patient had a seizure, was confused and had *E. coli* bacteremia his prognosis was guarded. The CSF studies in GNBM show leukocyte counts ranging from 0-80,600 cells/mm^3, with polymorphonuclear leukocytes accounting for more than 50% of the total in 90% of cases.[2] The CSF glucose concentration is usually low in GNBM. Nearly three-quarters of patients with GNBM have CSF to blood glucose concentration ratio less than 50% and CSF protein exceeds 200 mg/dL in 62% cases with mean values ranging from 171-1123mg/dl.[2] These results concurred with our case (**Table 1**). Gram stain is positive for GNBM in more than 50% of adult patients. The CSF culture is essential to establish the etiology of meningitis and to determine the antimicrobial susceptibilities of the pathogen.[1] Broad-spectrum cephalosporins have a high level of in vitro activity against Gram negative pathogens and penetrate extremely well into the CSF.[2] However, mono-therapy with a third generation cephalosporin should only be continued when the identity of the organism and its susceptibility patterns are known because of emergence of resistant strains. Local sensitivity patterns have to be taken into consideration since a recent series of *E. coli* meningitis from Senegal showed a 95% susceptibility to ceftriaxone, aztreonam, gentamicin, and ciprofloxacin.[4] Imipenem is the choice for cephalosporin-resistant organisms.[2] However, meropenem is generally advised as it does not share the epileptogenic potential of the former, and it has efficacy equivalent to that of cefotaxime for meningitis.[2,5] In our patient, who had suffered seizures, meropenem was an appropriate choice. Parental aminoglycosides are useful only when given with another bactericidal drug that penetrates the CSF well.[5] Despite good in vitro activity, meropenem therapy can fail because of the emergence of resistance during therapy.[5] We considered continuing gentamicin

Table 1 - Cerebrospinal fluid analysis.

Day	WBC	PMN %	Lymph %	Glucose (mg/dl) {Serum/CSF}	Proteins (mg/dl)	LDH (U/L)	Gram stain	Latex and India ink	Culture and sensitivity
1st day	140	92	8	72 (23%)	379	582	Negative	Negative	No growth (On 4th day)
6th day	2000	95	5	131 (56%)	161	660	Many pus cells and gram negative bacilli	Negative	*E. coli* (On 10th day)
14th day	50	20	80	131 (62%)	150	30	Negative	Negative	No growth (On 18th day)

WBC – white blood cell, PMN - polymorphonuclear, LDH – lactate dehydrogenase, CSF – cerebrospinal fluid, *E. Coli* – *Escherichia coli*

in addition to meropenem on that basis; CSF should be sampled again after 4 days of therapy as the average duration to sterilize CSF in adults is 2-4 days.[2]

There are no comparative studies of the duration of treatment in patients with GNBM. However, because of the high relapse rate in patients treated with shorter courses, one study recommended therapy to continue for at least 21 days.[5] Accordingly, we continued antibiotics for 21 days and the patient was discharged in a good health.

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