Treatment of *Elizabethkingia meningoseptica* Neonatal Meningitis with Combination Systemic and Intraventricular Therapy

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Abstract

Elizabethkingia meningoseptica, a gram negative bacillus ubiquitous in the hospital environment, is known to infrequently cause serious neonatal infections, particularly meningitis which is associated with high mortality and neuromorbidity in survivors. The authors describe a healthy term newborn with no apparent risk factors who developed *Elizabethkingia meningoseptica* sepsis and meningitis on day 6 of life. Diagnosis could be established only after a week of the illness by which time the baby developed refractory status epilepticus, ventriculitis and hydrocephalus. The isolate was susceptible to only ciprofloxacin, tigecycline and rifampicin and resistant to vancomycin. Apart from systemic combination therapy for 12 wk, intraventricular vancomycin was given through an external ventricular drain for 4 wk and later a ventriculo-peritoneal (VP) shunt was inserted. With this regime, authors demonstrated microbiologic and clinical cure. The baby is neurologically normal over a 6 mo follow-up.

Keywords *Elizabethkingia* · Meningitis · Intraventricular · Vancomycin · Neonate

Introduction

Elizabethkingia meningoseptica, previously known as *Chryseobacterium meningosepticum* till 2005 and *Flavobacterium meningosepticum* till 1994 is an ubiquitous Gram negative bacillus colonizing the hospital environment including sinks, water tanks, incubators, beds, saline solutions, syringes, feeding tubes, ventilator tubings, humidifiers among many other sites [1]. It has been associated with serious infections in newborns, patients in the intensive care unit and the immunocompromised. Newborn disease is predominantly meningitis, more common in the premature and often occurs as outbreaks [2]. Accurate diagnosis and susceptibility testing requires advanced microbiologic methods. Treatment

is challenging since the organism is resistant to most antimicrobials used for empirical therapy in neonatal sepsis/meningitis including beta lactams, carbapenems and aminoglycosides [3]. A recent review described a total of 283 published cases of *Elizabethkingia* infections in children, of which 35 cases were from India and more than three quarters were in neonates. Neonatal mortality was 37% and nearly 1/3rd of survivors had sequelae including hydrocephalus and other deficits [2].

The authors' share their experience of a newborn with severe *Elizabethkingia* meningitis that was successfully treated with prolonged intraventricular vancomycin therapy despite the isolate being resistant to it *in vitro*.

Case Report

A 6-d-old male, exclusively breastfed baby presented to another hospital with fever, vomiting and irritability of 1 d duration. He was born at term to a fourth gravida with two previous first trimester abortions by elective lower segment Cesarean section at a small maternity home with a birth weight of 3.5 kg. The baby was roomed in with the mother and exclusively breastfed and discharged at day 4 of life. There were no invasive procedures performed on the baby. At admission, the baby was sick looking but sepsis screen was negative. Treatment with

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intravenous cefotaxime and amikacin was initiated, but the symptoms persisted and by day 13 of life the baby developed seizures. A repeat sepsis screen showed a rise in WBC count and c-reactive protein (CRP). Cerebrospinal fluid (CSF) analysis was suggestive of bacterial meningitis with 2800 cells, 90% polymorphs, protein of 266 mg/dl and sugar of 36 mg/dl against a random blood sugar of 98 mg/dl. Antibiotics were upgraded to meropenem and the baby was referred to authors' hospital. The baby was intubated, ventilated and managed for refractory status epilepticus. The MRI Brain showed signs of meningitis, ventriculitis and hydrocephalus (Fig. 1). The lumbar puncture was repeated; both this CSF and the previous one grew Gram negative rods identified as *Elizabethkingia meningoseptica* by VITEK 2 and MALDI-TOF MS. The isolate was sensitive only to ciprofloxacin, tigecycline and rifampicin. The vancomycin MIC by E strip was 16 (susceptibility breakpoint 4). Treatment with intravenous ciprofloxacin (10 mg/kg twice daily), tigecycline (1.5 mg/kg twice daily), vancomycin (15 mg/kg thrice daily) and oral rifampin (10 mg/kg/d) was initiated. An external ventricular drain (EVD) was placed and vancomycin 10 mg was given daily through EVD followed by clamping of the drain for 6 h. Trough CSF vancomycin level was 76

microgram/ml. The baby improved, the CSF became culture negative 7 d after initiating therapy and the EVD removed after 2 wk of therapy. Soon after, the head circumference increased and baby became drowsy. Repeat MRI Brain showed increased hydrocephalus with a new infarct in the right thalamus. The EVD was re-introduced and intraventricular vancomycin was given for 2 more weeks (though the CSF cultures were sterile from the fresh EVD). The CSF cell count and protein improved over time but did not normalize. A VP shunt was subsequently inserted. Systemic antibiotics were continued for a total period of 6 wk and then oral ciprofloxacin and rifampicin continued for another 6 wk. At nine mo follow-up the baby is physically and neurodevelopmentally normal.

Discussion

This baby with early onset sepsis with *Elizabethkingia meningoseptica* probably acquired the infection from exposure to contaminated water at the maternity home. Since this pathogen is an uncommon cause of neonatal sepsis, the initial

Fig. 1 MRI brain showing meningitis, ventriculitis and hydrocephalus

empiric antimicrobial therapy employed in this case and that in usual practice were ineffective.

Elizabethkingia meningoseptica demonstrates *in vitro* resistance to many antibiotics [3]. There are no established CLSI breakpoints. Disc diffusion testing, VITEK and E strip are known to be inaccurate for susceptibility testing; broth microdilution is the preferred method [4]. Drugs known to be active and used successfully for therapy include cotrimoxazole, tigecycline, minocycline, quinolones, piperacillin, tazobactam, cefepime and drugs active against gram positive bacteria such as vancomycin and rifampicin [4–8]. There have however been reports of resistance, unreliable susceptibility and failure of vancomycin in treatment of *Elizabethkingia* infections [9].

Treatment with multiple drugs is not the usual norm in Gram negative meningitis. However multiple drugs were used in the index case for the following reasons 1) the newborn was extremely sick with impending risk of death or serious neurologic morbidity 2) results of susceptibility testing by VITEK are often unreliable 3) Combination antimicrobial therapy is recommended for *Elizabethkingia* 4) the CNS penetration of the some of the drugs used (tigecycline) is limited. The isolate in index patient was resistant to vancomycin, a drug which has been used with fair degree of success in previous reports. However, there was a possibility that the susceptibility results for vancomycin by VITEK/ E strip were inaccurate (The authors did not have access to broth microdilution). Hence vancomycin was used despite *in vitro* resistance. Further, it is possible to achieve high levels of drug with local therapy. Standard guidelines also recommend use of local intraventricular/ intrathecal therapy in resistant meningitis/ ventriculitis [10]. Successful treatment of *Elizabethkingia* meningitis with intraventricular vancomycin has been previously described [8] Hence intraventricular vancomycin was used in addition to systemic vancomycin. The duration of therapy was also longer than what is usually recommended for meningitis/ ventriculitis in view of the severity of disease, delayed response, persistent CSF and radiologic abnormalities.

This case highlights the need for appropriate infection control practices to prevent infections with this pathogen, correct identification and susceptibility testing and considering unconventional treatment approaches especially when therapeutic options are limited.

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Compliance with Ethical Standards

Conflict of Interest None.

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