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Case Report

Extensively drug-resistant acinetobacter baumannii meningitis which successfully treated with tigecycline; a case report of preterm newborn

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Abstract

Acinetobacter baumannii (A. baumannii) meningitis is a state difficult to treat with a high mortality rate, since antibiotics have low CSF penetration level and antibiotic resistance is frequently encountered. Multidrug-resistance is common in hospital-acquired *A. baumannii* infections, and in these cases, colistin treatment is frequently used as the last option. Colistin-resistant *A. baumannii* infections are reported in recent years.

We present a case of preterm newborn who developed extensively drug-resistant (carbapenem and colistin resistance) *A. baumannii* meningitis after ventriculoperitoneal shunt operation. Although not approved in children, combined intravenous treatment including tigecycline, meropenem and colistin provides clinical and bacteriological recovery in colistin and carbapenem-resistant *A. baumannii* meningitis.

Keywords: Acinetobacter; colistin; meningitis; tigecycline

INTRODUCTION

Acinetobacter species, which are aerobic and gram-negative coccobacillary bacteria, are important since they can stay alive for a long time and also have multidrug-resistance (MDR). They appear as important nosocomial pathogens in the hospital environment, causing epidemics at intervals (1).

Acinetobacter baumannii (A. baumannii) meningitis is a state difficult to treat with a high mortality rate, since antibiotics have low CSF penetration level and antibiotic resistance is frequently encountered. With the increase in the use of carbapenems as the first option in hospital-acquired sepsis, an increase is observed in carbapenem resistance. This situation has become a significant public health problem (2). Today, carbapenem resistance rate in hospital-acquired *A. baumannii* species is reported to be between 43.4 % and 62.4 % (3). In carbapenem-resistant *A. baumannii* cases, colistin and tigecycline are used as the last option. In addition, colistin-resistant acinetobacter infections have been reported in recent years (4, 5).

Only a few colistin-resistant *A. baumannii* meningitis cases have been reported in neonatal period (5). There aren't clear suggestions about treatment option and duration in these cases. We present a neonatal case developing colistin-resistant *A. baumannii* meningitis after ventriculoperitoneal shunt (VPS) operation. This case was successfully treated with a combination of tigecycline, colistin and meropenem.

CASE REPORT

A female infant who born at 30 weeks of gestation with birth weight of 1160 g, from a 29-years-old mother with an uneventful pregnancy. Her mother received antenatal steroid. The infant, who did not require resuscitation at birth, was given non-invasive ventilator support together with the surfactant treatment. Ampicillin and gentamicin treatment which were started empirically were discontinued on postnatal 3rd day due to the negative blood culture. Cranial ultrasonography examination was normal on postnatal 4th day. The nutrition of the patient, who was followed up in non-invasive ventilator support, was gradually increased. Hydrocephaly was found on postnatal 15th day in control cranial ultrasonography examination. Brain computerized tomography (CT) examination was taken when a pathological increase was observed in the patient around the head on postnatal the 22nd day. Dilatation was detected in CT examination in the third, fourth and lateral ventricules, and hemorrhage

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was seen in the right lateral ventricular posterior frontal horn (Figure 1). Subsequently, the VPS was placed. CSF examinations were normal (glucose 53 mg/dL, protein 84 mg/dL, and no cells were seen in direct microscopic examination). Brain CT examination was taken again when a pathological increase was observed in the patient around the head. Considering the shunt dysfunction, the tip of the shunt was freed. In CSF examination, glucose was detected to be <5 mg/dL, protein was 598.5 mg/dL, and intense leukocyte was seen in direct microscopic examination. *A. baumannii* was detected in CSF culture. Vancomycin and cefotaxime therapy which were started empirically were discontinued and meropenem (40mg/kg per dose three times a day) and colistin (3mg/kg per dose twice a day) therapy were started on postnatal 35th day. It was determined that the culture antibiogram, meropenem (mean inhibitory concentration (MIC) 32µg/mL) and colistin (MIC 4µg/mL) were resistant, while tigecycline (MIC 0.25µg/mL) was sensitive. Upon the continuation of CSF cell reaction and persistence of positive culture for *A. baumannii* on the 5th day of meropenem and colistin therapy, tigecycline (1.2 mg/kg per dose twice a day) was added to the existing therapy. CSF culture was negative in the follow-up. She was feeding with an orogastric tube and her interest in her environment was good. CSF protein and glucose levels returned to normal in the 6th week (Table 1).

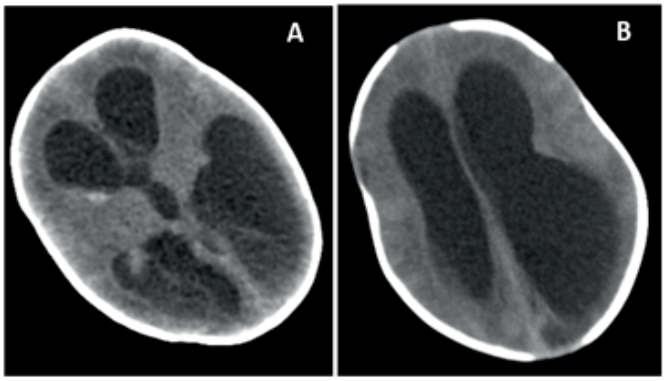

Figure 1. Preoperative axial CT scan of hemorrhage at the posterior frontal horn of right lateral ventricle (A) and dilated third, fourth and lateral ventricles (B)

In this period, the patient started peroral feeding. Following the meropenem and colistin therapy completed in 47 days and tigecycline therapy completed in 6 weeks, antibiotic therapy was discontinued. On postnatal 78th day, the patient's external ventricular drainage was taken out and VPS was placed. The patient was discharged at a weight of 2130 g with full oral feeding at postnatal 94th day. On post-discharge controls; the patient with a corrected age of 9 month was found to show developments compatible with her corrected age in detailed assessment conducted through the Bayley Scales of Infant Development Second Edition (Bayley-III).

Table 1. Weekly Biochemical Values and Culture results of Cerebrospinal Fluid During Acinetobacter Baumannii Meningitis Treatment.

Week	CSF glucose mg/dL	CSF protein mg/dL	CSF white blood cell / mm^3	CSF culture
1	<5	598.5	Intense leukocyte	A Baumannii
	<5	832	Intense leukocyte	A. Baumannii
2	<5	816	Intense leukocyte	A. Baumannii
	<5	750.1	600	-
3	<5	652.3	400	-
	<5	419.6	350	-
4	<5	400.1	200	-
	7	373	50	-
5	9	364.3	22	-
	11	305.8	8	-
6	14	262.5	0	-
	20	178.3	0	-
7	24	122	0	-
	34	97	0	-

*CSF=Cerebrospinal fluid

DISCUSSION

We present the case of a preterm newborn who developed meningitis after VPS operation caused by extensively drug-resistant *A. baumannii.* This case was treated with a combined therapy of colistin, tigecycline and meropenem.

In neonatal units, *A. baumannii* sepsis incidence has been reported to be between 8.3 % and 15.2 % (1,6). Since preterm infants are frequently exposed to long term central venous catheter, endotracheal intubation and other invasive interventions, they have 3-10 times higher acinetobacter infection incidence compared to term infants (7). Our case had prematurity, long term hospitalization and VPS placement all of which are risk factors for acinetobacter infection. Although *A. baumannii* is one of the rare agents of meningitis, its incidence has increased in postoperative meningitis cases. *A. baumannii* was detected in 3.6–11.2% of the cases which developed bacterial meningitis after

VPS operation (8). Additionally, CSF leak, head trauma, wound infection, long term mechanical ventilation and previous acinetobacter colonization are other risk factors that increase the frequency of meningitis (9).

Antimicrobial drug resistance in acinetobacter species has increased significantly in the last two decades (3). The existing intrinsic resistance of the organism against antibiotics, the ability of the relevant genes to acquire resistance quickly and being able to decrease the expression of external membrane play a significant role in this superior antimicrobial resistance ability of acinetobacter species (10).

There has not been too much clinical experience about the use of tigecycline in these MDR cases. In addition, enhanced tissue penetration leads to serum concentrations that may be well below the pharmacodynamics breakpoint and this can result in recurrent bacteremia. For this reason, colistin is mostly preferred in the treatment of carbapenem resistant-*A. baumannii* infections. Colistin, which is one of the polymyxin-group antimicrobials, has an ability to kill gram-negative bacteria quickly as well as acinetobacter species. Clinical and bacteriological success rate of intravenous and/or intraventricular colistin treatment in MDR *A. baumannii* meningitis was reported as 89% (11). However, with the increase of carbapenem resistant-*A. baumannii* cases, the use and resistance of colistin has also increased.

After the first colistin-resistant acinetobacter was reported in Czech Republic in 1999, colistin-resistant acinetobacter cases were reported throughout the world with a rapid increase (12). Although, colistin resistance rate in *A. baumannii* is reported less than 7% in most of the countries, there are very high resistance rates in some countries (40,6% in Spain and 30,6% in Korea) (4). Tigecycline has become the last option that can be used for extensively drug-resistant acinetobacter species. Tigecycline, which is a wide spectrum glycycline group antibacterial, binds to the 30S ribosomal sub-unit of bacteria, inhibits protein synthesis and stops bacterial proliferation. Tigecycline, which was used in the treatment of community-acquired pneumonia, complicated intraabdominal infections and skin infections in previous years, did not have an obvious superiority over other antimicrobials which are commonly used in the treatment of this kind of infections (13). For this reason, tigecycline was not a commonly used and obtainable drug. However, today tigecycline is frequently used in the treatment of bloodstream and central nervous system infections resulting from multidrug-resistant acinetobacterial and other factors (14). In fact, CSF penetration of tigecycline is not good. However, the success rate of tigecycline therapy seems to be sufficient in the treatment of children and neonates with meningitis (5). In an adult patient with acinetobacter meningitis who was using standard dose intravenous tigecycline, CSF concentration of tigecycline was shown to continue in a consistent level over MIC value (14). In our case, we were successful with only intravenous therapy without intraventricular treatment. As in our case, *A. baumannii* meningitis cases, who were treated with only intravenous tigecycline and colistin, were also reported (5). Combined antimicrobial therapy is recommended in resistant *A. baumannii* infections. Studies with tigecycline-containing combinations have found that tigecycline has a synergistic effect with colistin, levofloxacin, amikacin and imipenem/cilastatin (15). We used tigecycline with meropenem and colistin (although they were resistant).

Previous cases demonstrated that side effects such as nausea, vomiting and diarrhea increase during tigecycline therapy. In addition, tigecycline has been reported to induce acute pancreatitis (13). We did not observe these side effects during our patient's long term treatment. Liver and kidney functions of our patient, which we assessed at intervals, were found to have a normal course.

CONCLUSION

As the conclusion, although not approved in children, combined intravenous treatment including tigecycline, meropenem and colistin provides clinical and bacteriological recovery in colistin and carbapenem resistant-*A. baumannii* meningitis.

Conflict of interest: The authors declare that they have no competing interest.

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