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Use of Intraventricular Vancomycin in Neonatal Meningitis due to *Elizabethkingella meningoseptica*

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Abstract

Elizabethkingella meningoseptica is a non-motile, catalase positive, oxidase positive, non-glucose fermenting, gram negative bacilli which is resistant to common drugs active against gram negative organism. It manifests mainly as meningitis in newborns especially in preterms that are immune compromised. Antibiotics which have shown effectiveness against this organism includes cotrimoxazole, tigecycline, minocycline, quinolones, piperacillin, tazobactam, cefepime and drugs active against gram positive bacteria such as vancomycin and rifampicin. The major reason for the cautioned use of Intraventricular/Intrathecal therapy has been the significant toxicity that was reported by earlier studies. These included seizures in up to 20% of the patients and chemical ventriculitis in as high as 60% of the patients, though those were considered to be dose related. Few papers have also reported side effects such as transient hearing loss and seizures. Here we report a preterm newborn having *E. meningoseptica* ventriculitis showing improvement with intraventricular vancomycin without any short term adverse effect in first 6 months of life.

Keywords: *Elizabethkingella*; Meningitis; Intraventricular; Vancomycin; Neonate.

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 [3]. It manifest mainly as meningitis in newborn specially in preterms who are immune compromised [4]. It is resistant to most antimicrobials used for empirical therapy in neonatal sepsis/meningitis including beta lactams, carbapenems and aminoglycosides [5]. Neonatal mortality was 37% and nearly 1/3rd of survivors had sequelae including hydrocephalus and other deficits [4].

Here we report a case of *Elizabethkingella meningoseptica* causing neonatal meningitis in preterm neonate not responding to intravenous drugs as per blood culture and sensitivity, but responded well to intraventricular vancomycin..

Case Report

A pre-term 30 weeks 5 days gestation male baby was born to a gravida 2 para 1 mother with 1 live child, with birth weight of 1.266 kg. Baby was delivered by LSCS, done in view of uncontrolled PIH with non progression of labour. Baby cried soon after birth. As oxygen saturation was between 84-90% so baby was put on nasal CPAP ventilation in NICU. Chest X Ray done was suggestive of RDS, surfactant was administered. CPAP was weaned off by day 7 of life. Initially baby was kept NPO and IV fluid was started. Minimal OG feed and TPN was started on day 2 of life but baby could not tolerated OG feed, so pediatric surgeon opinion was taken and advised to do X-Ray abdomen erect and gastrographin study, which was suggestive of malrotation of intestine. Hence baby was operated for same on day 5 of life. Sepsis screen done on day 2 of life was positive, so Inj Cefotaxime and Inj Amikacin were started. Inj Metronidazole was added post surgery for malrotation on day 6 of life. On repeated sepsis screens CRP was increasing so on day 9 of life cefotaxime was stopped and Inj Piperacillin Tazobactam added which was further upgraded next day due to continuous increase in sickness. So baby was started on Meropenem and Amikacin in anti meningitic dose. Blood culture and ET culture showed growth of *Elizabethkingella meningoseptica* which was sensitive to vancomycin, so vancomycin was added on day 12 of life. Repeat Blood culture was also sent and again the same organism grown so

Introduction

Elizabethkingella meningoseptica was previously known as *Chryseobacterium meningosepticum* until 2005 and *Flavobacterium meningosepticum* until 1994 [1,2]. It belongs to group II a of Centers for Disease Control and Prevention (CDC) classification of previously unclassified bacteria and consists of yellow pigment producing non-motile, catalase positive, oxidase positive, non-glucose fermenting Gram-negative bacilli. It was first isolated in 1959 by Elizabeth O. King an American bacteriologist while she was working on unclassified bacteria associated with meningitis in infants at CDC Atlanta [3]. *Elizabethkingella meningoseptica* is an

meropenem was stopped as was resistant. Rifampicin and cefepime+tazobactam (antimeningitic dose) was added as per sensitivity. LP was done which was suggestive of meningitis and culture also showed the growth of the same organism, which was resistant to vancomycin and rifampicin. So vancomycin and Rifampicin were stopped and linezolid was added. After that, repeated lumbar punctures showed meningitis and culture also showed same organism sensitive to cefepime+tazobactam, linezolid. CSF culture on 19th day was also sensitive to Rifampicin so Rifampicin was again added on day 32 of life. As CSF was continuously growing same organism despite 18 days of sensitive antibiotics in adequate doses so 10 mg vancomycin was added intraventricularly although was not sensitive but was used in literature with similar setting. After 18 days of vancomycin intraventricularly, CSF culture was negative and gram's stain became negative for organism. Thereafter intraventricular vancomycin was stopped after 21 days.

USG cranium after diagnosis of meningitis showed ventriculomegaly. MRI was done which showed ventricular enlargement with leptomeningeal enhancement suggestive of meningitis. Neurosurgery opinion was taken and advised to continue conservative treatment initially but in view of increasing ventricular size right sided external ventricular drainage was done on day 38 of life which was replaced with omaya reservoir (left sided) after 5 days. Ventriculoperitoneal shunt was put on day 75 of life once CSF culture became sterile and biochemistry was within normal limits (**Figure 1**) attached below showing ventriculomegaly and shunts *in situ*.

On day 10 of life, baby had apnea and repeated desaturation, so was intubated and put on mechanical ventilator. Repeated chest x ray showed right upper zone opacity. After apnea baby also had poor perfusion so received normal saline boluses and started on dopamine which was gradually tapered and stopped after 3 days. After that baby was weaned off from ventilator on day 23 of life and shifted on oxygen by HHHFNC. Gradually settings of HHHFNC were decreased and baby weaned off from it on day 27 of life. Baby maintained saturation on room air without distress thereafter.

TPN was stopped on day 10 of life. OG feed was again started after 6th day of surgery and gradually progressed. IV fluid was stopped on day 23 of life and was on full OG feed. Oral feed was tried on day 29 of life and fully established by day 73 of life. At discharge baby was on full oral feeds and gaining weight.

Neurological behavior of the baby remained appropriate for gestational age at discharge. Occupational therapy was given during hospital stay and plan to continue during follow up too. Baby needs long-term neurodevelopmental follow-up.

Discussion

E. meningoseptica is an infrequent organism causing meningitis in immunocompromised individuals. The first case of infection by this organism in India was reported way back in

1988-89 as a pathogen causing neonatal meningitis. Subsequently, there have been various studies, which have reported this rare pathogen causing neonatal and adult meningitis, septicemia and endocarditis in patients admitted for medical causes [6-10]. *Elizabethkingia meningoseptica* is uncommon cause of neonatal sepsis and show resistance to many antibiotics. Antibiotics which have shown effectiveness against this organism includes cotrimoxazole, tigecycline, minocycline, quinolones, piperacillin, tazobactam, cefepime and drugs active against grampositive bacteria such as vancomycin and rifampicin [11]. There have been reports of resistance, to vancomycin in treatment of *Elizabethkingia* infections [12]. We too started treatment with these drugs as per blood culture sensitivity but despite 8 weeks of drug treatment Csf clearance of *Elizabethkingia meningoseptica* was not seen, so planned to give a trial for intraventricular vancomycin.

The CSF concentration of intraventricular administration of vancomycin of 20 mg in previous clinical trials showed that the concentration in the CSF is prolonged at a high level. The result was the same regarding the administration of 10mg. It is believed that the recommended trough level of CSF against *Staphylococcus aureus*, *S. epidermidis*, which is the major pathogenic bacteria of shunt infection, is 5 to 10 mg/L [13,14]. No conclusive study was found for dosage levels against *Elizabethkingilla*.

The major reason for the cautioned use of Intraventricular/ Intrathecal therapy has been the significant toxicity that was reported by earlier studies. These included seizures in up to 20% of the patients and chemical ventriculitis in as high as 60% of the patients, though those were considered to be dose related [15,16]. Few papers have also reported side effects such as transient hearing loss and seizures using gentamicin and vancomycin, though most recent studies have shown little or no serious adverse effects with the use of polymyxin B, colistin, and vancomycin [17]. Meropenem and netilmicin which were used by Remes et al. for the first time also showed no adverse effects [17]. In our study, we did not encounter any patient with any serious adverse effects which supports the safety of IVT/IT therapy if used in the correct dosage.

At the same time, the possibility of adverse effects due to an overdose is of concern along with after effects such as auditory disorders and central nervous system disorders. Intoxication region of the established concentration in the CSF and the critical region of adverse effects are unknown [18-20]. Some studies show that auditory disorders and central nervous system disorders decline by making the CSF concentration of vancomycin ≤ 20 mg/L [21]. So we decided to give vancomycin 10 mg intraventricularly in our patient. Regarding the interval of intraventricular vancomycin, administration in 12-24 hourly interval is the current regime. We decide to give 24 hourly. Intraventricular vancomycin was administered for 21 days. Csf culture done after 18 days course of intraventricular vancomycin was sterile [22].

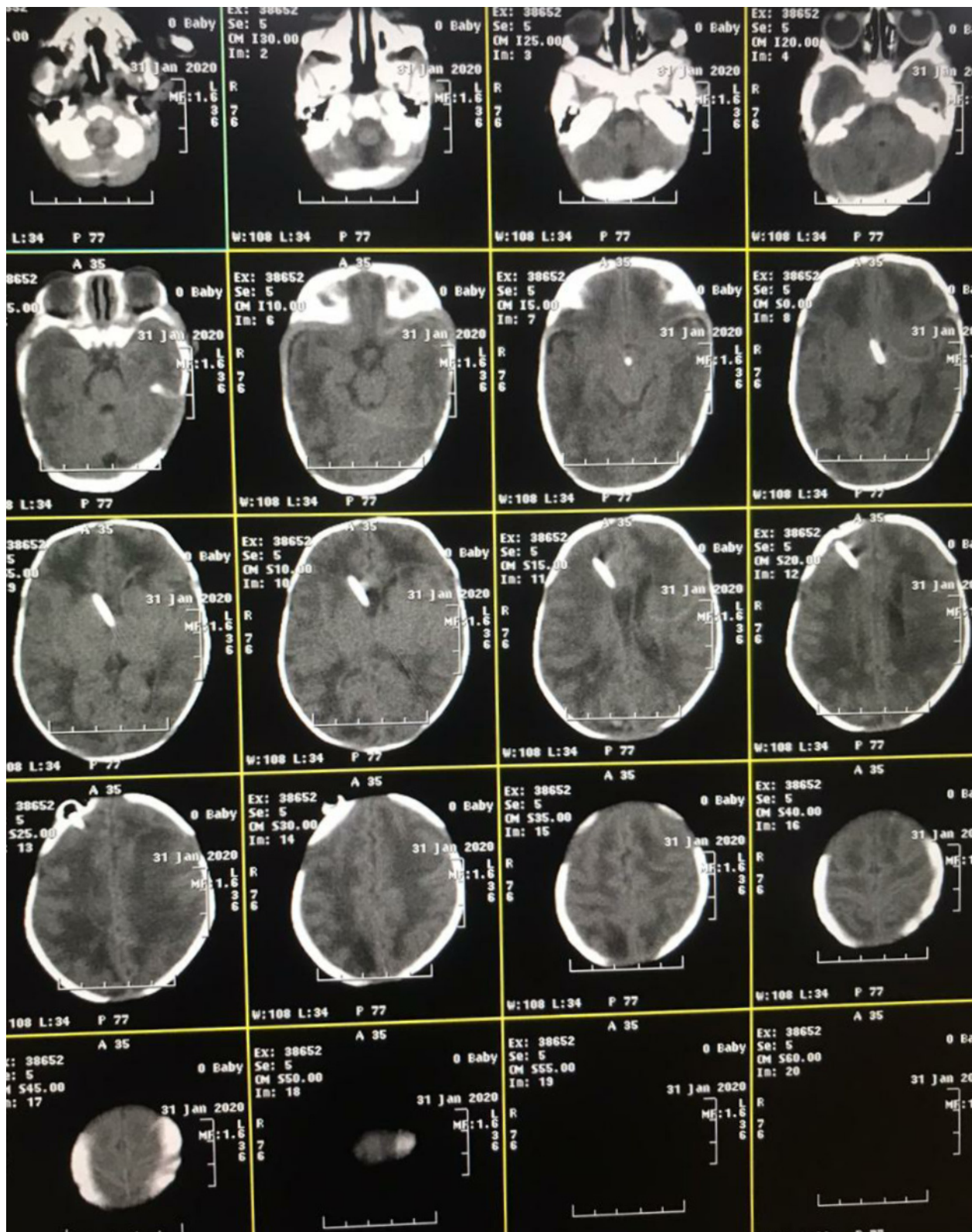


Figure 1: CT Brain showing VP shunt *in situ*.

Conclusion

Use of intraventricular vancomycin in neonates' especially preterm neonates needs more validation as data available is

not enough and needs time test trial. Long term neurological follow up needed to look for adverse effect of vancomycin over neurological behavior of infant over a period of time. Dose and duration of vancomycin needs clinical trial as per CSF concentration and time kill curve test. We got quick response

to vancomycin given intraventricularly, so will look for more detailed study in future if encountered with such resistant *Elizabethkingia meningoseptica* again.

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