Rare disease

Amplitude-integrated electroencephalography and MRI findings in a case of severe neonatal methicillin-resistant *Staphylococcus aureus* meningitis

Monika Olischar,¹ Rod W Hunt,² Andrew J Daley,³ Vanessa Clifford,³ David G Tingay²

¹Department of Neonatology, Children's University Hospital Vienna, Vienna, Austria

²Department of Neonatology, The Royal Children's Hospital, Melbourne, Victoria, Australia

³Department of Microbiology, The Royal Children's Hospital, Melbourne, Victoria, Australia

Correspondence to Monika Olischar, monika.olischar@meduniwien.ac.at

Summary

Methicillin-resistant *Staphylococcus aureus* (MRSA) can cause serious infection among hospitalised patients. The emergence of community acquired strains of MRSA (CA-MRSA) increases the potential exposure of newborns. The high incidence of reported meningitis in neonates in large CA-MRSA outbreaks suggests increased virulence in the neonatal population. The authors describe a case of severe meningitis due to MRSA in a previously healthy neonate and include findings from amplitude-integrated electroencephalography (aEEG) and MRI.

BACKGROUND

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a bacterium causing infection among patients in healthcare settings (usually multidrug resistant), and more recently, in the community (usually not multidrug resistant).¹ MRSA can cause invasive disease, with community acquired MRSA (CA-MRSA) being an increasingly common cause of soft tissue and bone infection, especially in adults.² In contrast, severe invasive infections in neonates are very rare but have been reported in the central nervous system.³ This is not surprising as the sick neonate is at increased risk of invasive infection due to impaired immunity, prolonged hospital admission, invasive procedures and long-term indwelling devices (surgery, central vascular access, mechanical respiratory support and drains).³

Regardless of the underlying pathogen, bacterial meningitis in the neonate remains a serious disease with significant long-term morbidity. Therefore, assessment of outcome is essential to help clinical decision making, for provision of accurate information to families and for identification of those patients who require intervention and early follow-up. Electroencephalograms (EEGs) have been used to predict the outcome of perinatal asphyxia, intraventricular haemorrhage and cerebral infarcts.^{4–5} Continuous neurological monitoring is important in at-risk infants in general, especially in subjects who are ventilated and sedated which makes clinical assessment difficult. Amplitude-integrated electroencephalography (aEEG) is being increasingly used to monitor cerebral activity at the bedside in the neonatal intensive care unit (NICU).⁶ Widely used scoring systems for aEEG consider background activity, sleep–wake cycling (SWC) and seizures.⁷ aEEG has been shown to predict outcome in sick newborns, especially those with hypoxic–ischaemic encephalopathy.⁸ Therefore, aEEG may be a useful prognostic tool for neonates with clinically severe bacterial meningitis.

Meningitis may also have profound effects on the brain parenchyma and neuroimaging plays an important role in the early diagnosis and characterisation of neurological complications.⁹ MRI is now used wherever available.

MRSA is a rare pathogen which is variably invasive and can be multidrug resistant, making prognosis difficult. We describe a case of severe meningitis and sepsis due to MRSA in a previously healthy neonate including, for the first time, aEEG and MRI findings. We received written consent from the parents to use their child's data.

CASE PRESENTATION

A 6-week-old male infant born at 33 weeks' gestation (birth weight 2320 g), who had been at home for 4 weeks, presented to a peripheral hospital with a 2-day history of lethargy, irritability and poor feeding. On examination he was febrile (38.6 °C) with a high pitched cry, a full fontanelle and frequent self-resolving focal tonic seizures involving the right arm and right leg. These were associated with eye and head deviation to the left and lasted less than 10 s. The seizure activity continued despite 20 mg/kg of phenobarbitone, 15 mg/kg of phenytoin and an intravenous midazolam infusion (1 mg/kg/h). He required mechanical respiratory support, muscle relaxation and sedation. Attempts at lumbar puncture prior to antibiotics were unsuccessful. Initially penicillin, cefotaxime, gentamicin and acyclovir were commenced. Over the course of the next 24 h the infant developed septic shock and required inotropic circulatory support.

A lumbar puncture was performed on admission to the NICU (24 h after the commencement of antibiotics) at The Royal Children's Hospital 30 h after presentation at the peripheral hospital. This showed a white cell count of $4750 \times 10^6/l$ (polymorphs 2250, lymphocytes 2500), a red cell count of $8000 \times 10^6/l$, glucose <1.1 mmol/l and a protein of 2.04 g/l. Bacterial culture was negative at 48 h and PCR

Figure 1 aEEG performed 24 h after admission showing a flat trace on both hemispheres.

Figure 2 Conventional T2 weighted MRI and apparent diffusion coefficient (ADC) map obtained from diffusion weighted imaging of the brain, showing severe generalised parenchymal oedema causing indistinct grey–white differentiation in both cerebral hemispheres and basal ganglia with profound global hypoxic insult.

for enterovirus and herpes simplex virus was also negative. The initial C-reactive protein was 230 mg/l (normal range <8 mg/l). Blood film showed 1.2 bands and an I/T ratio of 0.70, neutrophils 1.00 and lymphocytes 4.90; blood cultures collected prior to antibiotics grew MRSA (sensitive to vancomycin, clindamycin and ciprofloxacin). Thus, a presumed diagnosis of MRSA septicaemia with meningitis was made and antibiotics were rationalised to intravenous vancomycin.

Because of ongoing intermittent clinical seizure activity, aEEG monitoring was commenced on arrival. Over the following days the infant's encephalopathy deteriorated and he developed clinical status epilepticus despite loading with

phenobarbitone and ongoing midazolam infusion, whereas aEEG showed a flat trace over the entire 2 days of recording (figure 1). aEEG monitoring was therefore discontinued after 48 h.

MRI (conventional MRI and diffusion weighted imaging) of the brain (figure 2) performed on day 5 after admission showed extensive abnormality with severe generalised parenchymal oedema causing indistinct grey–white differentiation in both cerebral hemispheres and basal ganglia consistent with a profound left hemispheric hypoxic insult.

Furthermore, the patient also developed proptosis of the left eye and diabetes insipidus. Given the high likelihood of mortality and the poor neurodevelopmental prognosis

indicated by the aEEG and MRI findings, the parents elected to withdraw intensive care support on day 6 of admission. The infant died shortly thereafter.

DISCUSSION

We describe an uncommon presentation of severe meningitis in a neonate with MRSA sepsis.

Neonatal MRSA meningitis

S aureus is a nosocomial pathogen but a less frequent cause of late onset sepsis. A surveillance study of systemic late-onset sepsis (septicaemia or meningitis) in 11 Australian and New Zealand neonatal units revealed only 26 episodes of *S aureus* septicaemia out of 320, of which only one was due to MRSA.¹⁰ Recently, more invasive CA-MRSA infections have emerged. This increases the risk of exposure for newborn infants. Large outbreaks of serious CA-MRSA infections have been reported in neonatal units.^{11 12}

While a rare bacterium in the neonatal population, MRSA is an increasingly common cause of infection in the older population. The healthcare setting has traditionally been the source of MRSA infection. CA-MRSA has become an increasingly common cause of paediatric infection compared to healthcare associated MRSA.¹³ Most frequently, CA-MRSA causes skin and soft tissue infections,¹ while life-threatening infections such as necrotising pneumonia are rare.¹² However, there are reports demonstrating the potential high virulence of CA-MRSA in paediatric patients. In particular, MRSA is highly virulent in vulnerable hosts, including the immunocompromised and the newborn infant.¹¹

Recent reports have described the emergence of MRSA, including CA-MRSA, in NICUs. A report of a NICU outbreak of MRSA in a New York hospital involved nine low birthweight infants, was associated with serious infection and included four episodes of meningitis.³ Another isolated NICU invasive CA-MRSA outbreak in Israel illustrated how a rare community pathogen could rapidly spread via nosocomial transmission.¹² A retrospective study of MRSA isolates from infants in a tertiary care NICU in Houston, Texas, identified an emerging trend for CA-MRSA strains causing neonatal disseminating sepsis with substantial morbidity and mortality. In this study, one patient presented with central nervous system involvement showing cystic changes in the midbrain and ventriculomegaly with multiple septations within the ventricles.¹¹

Neonatal MRSA infection in our hospital (a large tertiary paediatric hospital) is relatively rare. In the years 1999–2008 there have been two others cases of MRSA bacteraemia, and no other cases of meningitis. There were a total of 22 superficial neonatal MRSA infections (13 involving the skin, five the eye, and four the respiratory system) over this period with no statistically significant change in the annual frequency of approximately 5% of all inpatient MRSA infections.

The source of infection in our case is unclear. It is possible that our patient acquired MRSA through cross-contamination from patients or staff during his initial hospital stay for prematurity.^{1 14} In a large series of infants with *S aureus* bacteraemia, those with CA-MRSA presented early in all cases.¹⁵ Our case was late onset. Community acquisition is also possible and parent-to-infant transmission has been described.¹⁶ Finally, transmission through contami-

nated breast milk has been described.¹⁷ The local hospital MRSA epidemiology and the length of time from discharge to rehospitalisation favour the hypothesis of an 'out of hospital' source.

Unfortunately, MRSA is usually not susceptible to standard empiric antibiotic therapy, particularly the initial therapy recommended in most guidelines for neonatal sepsis, as illustrated in our case. The two other invasive isolates identified in our hospital between 1998 and 2008 were multi-antibiotic resistant, including clindamycin and ciprofloxacin. Of the 22 superficial infections, 11 were with CA-MRSA, being sensitive to clindamycin. The authors of a large prospective cohort study of patients with MRSA concluded that clinicians should be aware that β -lactam antimicrobials can no longer be relied on as empiric therapy for severely ill outpatients whose infections may be staphylococcal in origin.¹⁸ In addition, there is some concern about the adequacy of vancomycin in achieving adequate levels in the cerebrospinal fluid (CSF). Munckhof *et al*¹⁹ described an adult patient with cavernous sinus thrombosis and meningitis caused by CA-MRSA and suggested that high doses of vancomycin might be required to achieve even low levels in the CSF. This observation relates to adult vancomycin pharmacokinetics; however, not much is known about pharmacokinetics in neonates, although in premature babies penetrance to CSF seems to be much higher than in adults.²⁰ Alternative therapies for MRSA meningitis, such as linezolid, have been proposed, but comparative efficacy and safety in neonates has not been assessed in a controlled setting. Given the rapid and fulminant course of our case, it is possible that delayed effective therapy influenced outcome, highlighting the importance of considering MRSA early.

The role of aEEG and MRI in assessing prognosis in neonatal meningitis

The use of electrophysiology for the assessment of the extent of any cerebral insult in the neonatal population is important. Recognised predictors of adverse outcome of neonatal bacterial meningitis include severity of clinical presentation, intensity of medical support required, laboratory abnormalities and abnormal EEG patterns. EEG patterns in the neonate are considered to be non-specific with respect to the aetiology of the disease.²¹

Neonatal meningitis, especially when of bacterial origin, carries a high risk of death or severe neurological sequelae. Despite declines in mortality, morbidity did not change significantly between the 1970s and 1990s.²² Shock, respiratory failure, focal neurological deficits or a positive CSF culture after 48–72 h of appropriate antibiotic therapy have all been associated with a higher morbidity.²³ Early predictors of adverse outcome at 1 year of age have been identified by Klinger *et al* and described for various time points. At 12 h after admission, poor prognostic markers include the presence of seizures, coma, use of inotropes and leucopenia. At 72 h after admission, ongoing seizure activity, coma and use of inotropes were ominous markers. Leucopenia at 96 h after admission was also a poor prognostic marker. There was no difference in outcome by pathogen.²⁴ Another group who studied early prediction of neurological sequelae or death after bacterial meningitis, developed a predictive score based on clinical findings, including gender, atypical convulsions in the history, low body temperature at admission and the pathogen.²⁵

In addition to a detailed clinical examination, electrophysiological tests of brain function should be performed.

An assessment of the contribution of EEG findings early in the course of neonatal bacterial meningitis to the prediction of severe adverse outcome showed that infants with normal or mildly abnormal EEGs had good outcomes, whereas those with moderate to markedly abnormal EEGs died or survived with adverse outcome.^{26 27} Continuous EEG recordings using aEEG also may be a useful prognostic tool for neonates with clinically severe bacterial meningitis. Previous studies have shown that the background pattern of the aEEG has been validated against conventional EEG^{28 29} and aEEG is now widely used as a continuous bedside monitoring tool for term and preterm babies.

aEEG has been shown to be a reliable and early predictor of outcome in preterm infants with intraventricular haemorrhage, focusing on the degree of background activity depression and the recovery of SWC.^{30 31} Furthermore, in term newborns with hypoxic-ischaemic encephalopathy, aEEG has become an essential tool in the prediction of later neurodevelopment. The sooner background activity normalises and the earlier sleep-wake cycles can be discerned in the course of a hypoxic cerebral insult, the better the chances for a good clinical recovery.^{13 32–34} In general, poor prognostic indicators include burst suppression, continuous low voltage or flat/isoelectric tracing. Low voltage can also predict adverse developmental outcome.³⁵

In our case, aEEG showed a flat trace 24 h after admission and did not change over the 48 h of the recording. A burst suppression pattern on aEEG has been described with the use of midazolam in the context of neonatal encephalopathy, however the flat trace observed in our patient is highly unlikely to be the result of drugs alone. This flat trace throughout the entire aEEG measurement is in contrast to the clinical status epilepticus of our patient. We hypothesise that the extent of the brain damage at the time of recording of cortical activity using aEEG could have been the reason that the firing of the neurons was not transmitted to the cortex and therefore monitored with aEEG.

The role of neuroimaging in central nervous system (CNS) infections needs to be elucidated. CNS infections are particularly challenging because imaging may demonstrate both evidence of the infection itself and the complications secondary to it, including cerebral infarction. It has been suggested that diffusion weighted imaging is more sensitive than conventional MRI alone in detecting changes due to infections and ischaemic lesions. Small cortical or deep white matter infarcts resulting from septic vasculitis are not easily recognised on routine imaging and diffusion weighted imaging may be more useful.³⁶ Jan *et al* showed that diffusion weighted imaging is a simple way of examining the vascular and neurological complications of bacterial meningitis.

In our case, both conventional MRI and diffusion weighted imaging showed restriction of diffusion in both hemispheres, suggesting patchy ischaemia in the left hemisphere and established right hemispheric infarction. These findings are similar to those of Shah and coworkers in six newborns with *Escherichia coli* meningitis.³⁷ The authors describe significant white matter injury on MR imaging in all patients.

Even though MRI provides additional important information highlighting the vulnerability of the cerebral white matter in CNS infections in the newborn infant, the prognostic value of this information remains unclear.

Learning points

- This case highlights the emerging importance of community acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) infections in the vulnerable neonatal population.
- The report serves as a reminder that meningitis can be a serious presentation of CA-MRSA infection in previously healthy neonates.
- Timely assessment of outcome is important to aid clinical decision making, for provision of accurate information to families and for identification of individuals who need intervention and early follow-up.
- aEEG and MRI findings may be useful when discussing further therapy and management with parents.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. **Elston DM.** Community-acquired methicillin-resistant *Staphylococcus aureus*. *J Am Acad Dermatol* 2007;**56**:1–16; quiz 17–20.
2. **Moran GJ,** Krishnadasan A, Gorwitz RJ, *et al.* Methicillin-resistant *S. aureus* infections among patients in the emergency department. *N Engl J Med* 2006;**355**:666–74.
3. **Noel GJ,** Kreiswirth BN, Edelson PJ, *et al.* Multiple methicillin-resistant *S. aureus* strains as a cause for a single outbreak of severe disease in hospitalized neonates. *Pediatr Infect Dis J* 1992;**11**:184–8.
4. **Mercuri E,** Rutherford M, Cowan F, *et al.* Early prognostic indicators of outcome in infants with neonatal cerebral infarction: a clinical, electroencephalogram, and magnetic resonance imaging study. *Pediatrics* 1999;**103**:39–46.
5. **Sinclair DB,** Campbell M, Byrne P, *et al.* EEG and long-term outcome of term infants with neonatal hypoxic-ischemic encephalopathy. *Clin Neurophysiol* 1999;**110**:655–9.
6. **Shah DK,** de Vries LS, Hellström m-Westas L, *et al.* Amplitude-integrated electroencephalography in the newborn: a valuable tool. *Pediatrics* 2008;**122**:863–5.
7. **Hellström-Westas L,** Rosén I, de Vries LS, *et al.* Amplitude-integrated EEG classification and interpretation in preterm and term infants. *NeonReviews* 2006;**7**:e76–e87.
8. **Toet MC,** Hellström m-Westas L, Groenendaal F, *et al.* Amplitude integrated EEG 3 and 6 hours after birth in full term neonates with hypoxic-ischaemic encephalopathy. *Arch Dis Child Fetal Neonatal Ed* 1999;**81**:F19–23.
9. **Counsell SJ,** Tranter SL, Rutherford MA. Magnetic resonance imaging of brain injury in the high-risk term infant. *Semin Perinatol* 2010;**34**:67–78.
10. **Isaacs D,** Barfield C, Clothier T, *et al.* Late-onset infections of infants in neonatal units. *J Paediatr Child Health* 1996;**32**:158–61.
11. **Healy CM,** Hultén KG, Palazzi DL, *et al.* Emergence of new strains of methicillin-resistant *Staphylococcus aureus* in a neonatal intensive care unit. *Clin Infect Dis* 2004;**39**:1460–6.
12. **Regev-Yochay G,** Rubinstein E, Barzilai A, *et al.* Methicillin-resistant *Staphylococcus aureus* in neonatal intensive care unit. *Emerging Infect Dis* 2005;**11**:453–6.
13. **Buckingham SC,** McDougal LK, Cathey LD, *et al.* Emergence of community-associated methicillin-resistant *Staphylococcus aureus* at a Memphis, Tennessee Children's Hospital. *Pediatr Infect Dis J* 2004;**23**:619–24.
14. **Bertin ML,** Vinski J, Schmitt S, *et al.* Outbreak of methicillin-resistant *Staphylococcus aureus* colonization and infection in a neonatal intensive care unit epidemiologically linked to a healthcare worker with chronic otitis. *Infection Control Hosp Epidemiol* 2006;**27**:581–5.

15. **Kuint J**, Barzilai A, Regev-Yochay G, *et al*. Comparison of community-acquired methicillin-resistant *Staphylococcus aureus* bacteremia to other staphylococcal species in a neonatal intensive care unit. *Eur J Pediatr* 2007;**166**:319–25.
16. **Al-Tawfiq JA**. Father-to-infant transmission of community-acquired methicillin-resistant *Staphylococcus aureus* in a neonatal intensive care unit. *Infect Control Hosp Epidemiol* 2006;**27**:636–7.
17. **Gastelum DT**, Dassey D, Mascola L, *et al*. Transmission of community-associated methicillin-resistant *Staphylococcus aureus* from breast milk in the neonatal intensive care unit. *Pediatr Infect Dis J* 2005;**24**:1122–4.
18. **Naimi TS**, LeDell KH, Como-Sabetti K, *et al*. Comparison of community- and health care-associated methicillin-resistant *Staphylococcus aureus* infection. *JAMA* 2003;**290**:2976–84.
19. **Munckhof WJ**, Krishnan A, Kruger P, *et al*. Cavernous sinus thrombosis and meningitis from community-acquired methicillin-resistant *Staphylococcus aureus* infection. *Intern Med J* 2008;**38**:283–7.
20. **Reiter PD**, Doron MW. Vancomycin cerebrospinal fluid concentrations after intravenous administration in premature infants. *J Perinatol* 1996;**16**:331–5.
21. **Lerique-Koechlin A**. EEG in neonatal meningitis and cerebral hemorrhages. In: Remond A, ed. *Handbook of Electroencephalography and Clinical Neurophysiology*. Amsterdam: Elsevier 1972:53–61.
22. **Unhanand M**, Mustafa MM, McCracken GH Jr, *et al*. Gram-negative enteric bacillary meningitis: a twenty-one-year experience. *J Pediatr* 1993;**122**:15–21.
23. **Heath PT**, Nik Yusoff NK, Baker CJ. Neonatal meningitis. *Arch Dis Child Fetal Neonatal Ed* 2003;**88**:F173–8.
24. **Klinger G**, Chin CN, Beyene J, *et al*. Predicting the outcome of neonatal bacterial meningitis. *Pediatrics* 2000;**106**:477–82.
25. **Oostenbrink R**, Moons KG, Derksen-Lubsen G, *et al*. Early prediction of neurological sequelae or death after bacterial meningitis. *Acta Paediatr* 2002;**91**:391–8.
26. **Chequer RS**, Sharp BR, Dreimane D, *et al*. Prognostic value of EEG in neonatal meningitis: retrospective study of 29 infants. *Pediatr Neurol* 1992;**8**:417–22.
27. **Klinger G**, Chin CN, Otsubo H, *et al*. Prognostic value of EEG in neonatal bacterial meningitis. *Pediatr Neurol* 2001;**24**:28–31.
28. **Toet MC**, van der Meij W, de Vries LS, *et al*. Comparison between simultaneously recorded amplitude integrated electroencephalogram (cerebral function monitor) and standard electroencephalogram in neonates. *Pediatrics* 2002;**109**:772–9.
29. **Shellhaas RA**, Gallagher PR, Clancy RR. Assessment of neonatal electroencephalography (EEG) background by conventional and two amplitude-integrated EEG classification systems. *J Pediatr* 2008;**153**:369–74.
30. **Olischar M**, Klebermass K, Waldhoer T, *et al*. Background patterns and sleep-wake cycles on amplitude-integrated electroencephalography in preterms younger than 30 weeks gestational age with peri-/intraventricular haemorrhage. *Acta Paediatr* 2007;**96**:1743–50.
31. **Hellstr m-Westas L**, Klette H, Thorngren-Jerneck K, *et al*. Early prediction of outcome with aEEG in preterm infants with large intraventricular hemorrhages. *Neuropediatrics* 2001;**32**:319–24.
32. **van Rooij LG**, Toet MC, Osredkar D, *et al*. Recovery of amplitude integrated electroencephalographic background patterns within 24 hours of perinatal asphyxia. *Arch Dis Child Fetal Neonatal Ed* 2005;**90**:F245–51.
33. **Osredkar D**, Toet MC, van Rooij LG, *et al*. Sleep-wake cycling on amplitude-integrated electroencephalography in term newborns with hypoxic-ischemic encephalopathy. *Pediatrics* 2005;**115**:327–32.
34. **ter Horst HJ**, Sommer C, Bergman KA, *et al*. Prognostic significance of amplitude-integrated EEG during the first 72 hours after birth in severely asphyxiated neonates. *Pediatr Res* 2004;**55**:1026–33.
35. **Tao JD**, Mathur AM. Using amplitude-integrated EEG in neonatal intensive care. *J Perinatol* 2010;**30**(Suppl):S73–81.
36. **Jan W**, Zimmerman RA, Bilaniuk LT, *et al*. Diffusion-weighted imaging in acute bacterial meningitis in infancy. *Neuroradiology* 2003;**45**:634–9.
37. **Shah DK**, Daley AJ, Hunt RW, *et al*. Cerebral white matter injury in the newborn following *Escherichia coli* meningitis. *Eur J Paediatr Neurol* 2005;**9**:13–17.

This pdf has been created automatically from the final edited text and images.

Copyright 2010 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Olischar M, Hunt RW, Daley AJ, Clifford V, Tingay G. Amplitude-integrated electroencephalography and MRI findings in a case of severe neonatal methicillin-resistant *Staphylococcus aureus* meningitis. *BMJ Case Reports* 2010;10.1136/bcr.02.2010.2729, date of publication

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow