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Case Report

Early-onset neonatal sepsis caused by *Neisseria meningitidis* serogroup B: case report and literature review of a 102-year period

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ABSTRACT

A 36-week-2-day-old male infant was admitted to the neonatal unit with respiratory distress, hypoglycaemia and suspected early onset neonatal sepsis for respiratory support, monitoring and intravenous antibiotics. His initial C-reactive protein was 12 mg/L, this increased to 66 mg/L at 24 hours. Blood cultures at 48 hours confirmed *Neisseria meningitidis* serogroup B. As the isolate was sensitive to benzylpenicillin the same antibiotic was continued for a total of 7 days. His mother remained asymptomatic but was monitored closely. Ciprofloxacin chemoprophylaxis was given to close family contacts. *Neisseria meningitidis* causing early onset neonatal sepsis is extremely rare and neonates may have minimal symptoms at presentation. A table reviewing all documented cases of early onset neonatal sepsis caused by *Neisseria meningitidis* over a 102-year time period is included. There is need for early identification and initiation of empirical antibiotic therapy pending confirmation and sensitivities.

Key words: neonatal sepsis, *Neisseria meningitidis*, invasive meningococcal disease, antibiotics, chemoprophylaxis.

Neonatal sepsis is defined as 'a systemic inflammatory response syndrome specifically presenting with abnormalities of temperature and/or leukocytosis in an infant from birth to 4 weeks of age as a result of proven infection'.[1] It can present as neonatal meningitis, septicaemia or a combination of both. Early onset neonatal sepsis (EOS) presents in the first 6 days of life with late onset neonatal sepsis presenting at 7–28 days.[1] A prospective multicenter surveillance study involving 12 English neonatal units over 3 years (2006-2008) with 124 confirmed isolates reported the most common organisms responsible for EOS were: Group B Streptococcus (GBS) (50%), *Escherichia coli* (18%), *Listeria monocytogenes* (6%), Streptococcus spp. (6%) and *Staphylococcus aureus* (5%).[2] The same study also reported the incidence of EOS at 0.9/1,000 live births.[2]

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Neisseria meningitidis causes invasive meningococcal disease (IMD). Although rare in developed countries, it remains one of the most feared infectious diseases. A data linkage project by Public Health England estimated the total burden of IMD in England to be 5,115 laboratory-confirmed cases over a five-year period (2007-2011) with group B meningococci responsible for 87.33% (n: 4,034) of hospitalised cases.[3] The same study reported that infants (<1 year-old) accounted for 1,115/4,619 (24.14%) of cases, although no specific further breakdown for neonates were given. *Neisseria meningitidis* as a causative organism in EOS is extremely rare.[4,5] This article describes a case of early onset neonatal sepsis caused by *Neisseria meningitidis*.

Case Report

A 36-week-2-day-old male was born following a normal vaginal delivery, with poor respiratory effort, tachycardia, pallor and hypotonia. The neonate was resuscitated via face mask

with a T-piece used to deliver intermittent positive pressure ventilation. As the neonate's spontaneous respiratory effort remained inadequate, he was started on positive end expiratory pressure of 5-8 cm water pressure and transferred to the neonatal unit. Initial neonatal blood gases demonstrated a respiratory acidosis (pH 7.11; $PaCO_2$ 12kPa).

On admission his temperature was 37.3˚C, pulse rate 140/min, respiratory rate 44/min, and blood pressure 59/39 mmHg. Blood glucose on admission was 1.1 mmol/L (19.8 mg/dl) and a 10% dextrose bolus of 2 ml/kg was administered. No maternal risk factors were identified. However, clinical indicators for possible EOS included: a) altered behaviour/ responsiveness b) tachycardia c) signs of respiratory distress syndrome (RDS) needing CPAP support d) prematurity e) hypoglycaemia.

Routine blood investigations and blood cultures were obtained, and the neonate was commenced on intravenous benzylpenicillin (50 mg/kg/dose twice daily) and gentamicin (5 mg/kg/dose 36 hourly). Chest X-ray demonstrated moderate RDS. C-reactive protein (CRP) was 12 mg/L increasing to 66 mg/L at 24 hours; a white blood cell count of $4.6x10^9$/L increasing to $13.2x10^9$/L. Blood gases improved as did blood glucose. He was weaned off CPAP at 24 hours.

CSF samples obtained at 31 hours of age showed no evidence of meningitis. Blood cultures at 48 hours identified *Neisseria meningitidis* serogroup B. Following a discussion with a medical microbiologist and as the neonate was improving clinically, penicillin was continued for a total of 7 days, and gentamicin was discontinued after the third dose. Antibiotic sensitivities confirmed that the organism was susceptible to penicillin [minimum inhibitory concentration (MIC) 0.06 mg/L] and cefotaxime (MIC 0.004 mg/L). His CRP had settled to 9 mg/L on day-5.

Close contact chemoprophylaxis with ciprofloxacin was prescribed for the parents and grandparents. The neonate was discharged at day-12 and reported as doing well at clinic follow-up few months later. Participation involved informed consent.

Discussion

The isolate from the neonate was *Neisseria meningitidis* group B type 1 (subtype NT/NT). IMD in neonates has been caused by all major serogroups of *Neisseria meningitidis* such as A, B, C, Y and W135.[4-8] However, literature reviews highlight the preponderance of *Neisseria meningitidis* serogroup B as the major causative agent in neonatal IMD.[4,6-9]

Koplick, in 1916, published the first case of neonatal meningococcal meningitis (NMM).[9] The exact incidence of *Neisseria meningitidis* as a causative agent for neonatal sepsis is not well known.[6] A review article reported 15/424 (3.5%) cases of confirmed neonatal bacterial meningitis in England and Wales that were due to *Neisseria meningitidis* over a 5-year period (1985-87, 1996-97).[10] A more recent study from France between 2001 and 2013 found that 23/831 (2.8%) cases of neonatal bacterial meningitis were caused by *Neisseria meningitidis*.[9]

A literature review conducted using the PubMed, Google Scholar, and Scirus databases revealed 21 published cases of EOS caused by *Neisseria meningitidis* over a 102-year period (1916 - 2018).[4,6,8,9,11] Table I highlights the clinico-pathological outcomes of 16 cases of EOS where adequate records were available. The 16 cases of EOS caused by *Neisseria meningitidis* were due to NMM (n: 7), septicaemia (n: 5) or a combination of both (n: 3). The mortality rate in neonates from EOS caused by *Neisseria meningitidis* was 40% (6/15) based on this literature review over the 102-year period.

A review of the literature by Kiray Baş et al.[4] identified significant risk factors for neonatal meningococcaemia which included: prematurity, maternal acute viral infections, functional asplenia, crowded environments, maternal smoking or neonates exposed to passive tobacco smoking. EOS cases caused

Table I. Clinico-pathological outcomes of early-onset neonatal sepsis caused by *Neisseria meningitidis* over a 102-year period (1916 - 2018).[4,6,8,9,11]

Author(s), year of publication	Day of onset	Clinical features in neonate	Maternal swab for *N. meningitidis*	Neonatal culture positive sample types	Sero-group Identified	Treatment	Outcomes
Koplick, 1916	3	-	N/A	CSF	N/A	Pre-antibiotic era	Survived, developed hydrocephalus
Carmona et al, 1953	2	-	N/A	CSF	N/A	Penicillin	Survived
Carmona et al, 1953	4	-	N/A	CSF	N/A	Penicillin	Survived
Kao et al, 1956	4	-	N/A	CSF	N/A	Penicillin, chloramphenicol, sulfadiazine	Died
Sunderland et al, 1972	1	Fever, irritability	Positive	CSF	C	Ampicillin, kanamycin	Died
Embree et al, 1987	1	-	N/A	CSF, blood	W135	Ampicillin, gentamicin	Survived
Chugh et al, 1988	3	Irritability	N/A	CSF	A	Penicillin, cefotaxime, gentamicin	Died
Bhutta et al, 1991	1	Hypotension, petechiae, prolonged resuscitation	N/A	Negative for neonate.	N/A	Penicillin, cefotaxime	Died Mother's blood and CSF cultures grew *N. meningitidis*
Ellis et al, 1992	3	Conjunctivitis	Positive	CSF, blood	C	Penicillin, cefotaxime	Survived
Ellis et al, 1992	3	Conjunctivitis	Positive	CSF, blood	W135	Penicillin, cefotaxime	Survived
Casanova et al, 2000	3	-	N/A	Blood	B	Penicillin	Survived
Lo et al, 2003	1	Petechiae	N/A	Blood	C	Ampicillin, gentamicin	Died
Shepard et al, 2003	5 cases (1 on day-0, 3 on day-1, 1 on day-6	N/A	N/A	N/A	Predominantly serogroup C	N/A	N/A
Kurlenda et al, 2010	1	Respiratory distress, convulsion	Positive	N/A	B	Penicillin, cefotaxime	Survived
Smith et al, 2015	5	Petechiae, unresponsive	N/A	Blood	β-lactamase negative *N. meningitidis*	N/A	Died
Bilal et al, 2016	1	N/A	N/A	CSF	N/A	N/A	N/A
Chacon-Cruz et al, 2017	3	Conjunctivitis, irritability, tachypnea, poor feeding	Positive	Blood	Y	Ceftriaxone	Survived
Our case	0	Respiratory distress, hypoglycaemia, hypotonia	N/A	Blood	B	Penicillin, Gentamicin	Survived

CSF: cerebrospinal fluid; N/A: not available.

by *Neisseria meningitidis* may have minimal symptoms as was the cases in 6/15 babies or may have minimal symptoms at presentation.[4] It is vital that based on risk factors, red flags and clinical suspicion for IMD, the neonate undergoes early investigations and empirical antibiotic therapy with intravenous benzylpenicillin and gentamicin is initiated. Depending on the response and clinical progress, the antibiotic regime may be changed to cefotaxime or another appropriate antibiotic based on the sensitivity profile. However, cases of meningococcal infection truly resistant to penicillin are extremely rare although the MIC as well as higher dosing need to be kept in mind.

In cases of IMD resulting in EOS, it is important to investigate genitourinary colonization of the mother and consider nasopharyngeal carriage among close contacts. Although the nasopharyngeal carriage rate is high in the community, IMD in neonates remains a rarity, possibly due to the protective effect of maternal antibodies passed on from mother to fetus *in-utero*.[4] However, prematurity and low birth weight could have an impact on this.[4] The availability of the immunizations in the UK against Meningococcal B and C as well as the quadrivalent vaccine could impact on the epidemiology of IMD in the future.

It is important to liaise with Public Heath England or similar national organizations and offer chemoprophylaxis to all close contacts including healthcare professionals who may have come into contact with the neonate's respiratory secretions.[4] The mother should also be monitored closely and if she becomes unwell or there is any suspicion of maternal sepsis, then blood cultures and appropriate antibiotic therapy e.g. intravenous ceftriaxone should be started promptly.

EOS due to IMD is extremely rare but can be life-threatening. Whilst rare, with symptom manifestation being atypical compared to older age groups, a raised index of suspicion should lead to prompt administration of appropriate intravenous antibiotics as well as taking blood/CSF cultures as this is likely to be associated with a better outcome. Further research is needed to facilitate a consensus, as currently there are no guidelines for empirical treatment of neonatal IMD.

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