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A newborn boy with fever and seizures

EDUCATIONAL CASE REPORT

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Background

Enteroviruses are common causes of infections in neonates. Enterovirus infections can present with mild and nonspecific symptoms but may also cause more severe disease, such as sepsis-like illness and meningitis. Distinguishing enterovirus infections from bacterial infections can be challenging. Consequently, patients may be given unnecessary broad-spectrum antibiotics, which is particularly undesirable in neonates.

Case presentation

A newborn boy, healthy at birth, developed fever in his first week of life. His clinical course fluctuated over several days, ultimately culminating in seizures. Blood cultures and cerebrospinal fluid analysis did not reveal a bacterial aetiology. However, enterovirus RNA was found in both serum and cerebrospinal fluid by polymerase chain reaction, confirming a diagnosis of enterovirus meningitis due to Coxsackievirus B5. Anticonvulsant therapy was initiated, antibiotics were discontinued, and the infant recovered without complications.

Interpretation

This case illustrates that the clinical presentation of enterovirus infections in neonates can be difficult to distinguish from other viral and bacterial infections. Greater awareness of enteroviruses as potential causes of severe neonatal infections, along with knowledge of appropriate testing, may facilitate accurate diagnosis and help avoid unnecessary antibacterial therapy.

A newborn boy was admitted to hospital with fever, lethargy, poor feeding and subsequently seizures. Following a challenging clinical course, a serious and clinically

significant underlying cause was identified. Prompt diagnosis was required to avoid unnecessary treatment.

The mother of a six-day-old boy contacted the postnatal ward. The infant had been lethargic and uninterested in feeding since discharge, with a rectal temperature of 38.4 °C over the past 24 hours. He was therefore referred to the paediatric department. He was born at 39 weeks gestational age following induction due to reduced fetal activity on cardiotocography. The pregnancy had otherwise been uncomplicated. The infant's Apgar scores were 9, 9 and 9, with a birth weight of 3710 g, length 49.5 cm and head circumference 34.5 cm. His stay in the postnatal ward had been unremarkable, and the findings from the paediatric examination on the second day of life had been normal.

On admission, the infant appeared irritable and difficult to soothe. He woke with high-pitched crying. Rectal temperature was 38.4 °C, with other vital signs within the normal range. His skin was cool and peripherally cyanosed, with a capillary refill time of two seconds. The pharynx was erythematous with mildly enlarged tonsils, without exudate. His weight was 10 % below birth weight. The findings were normal for the rest of the clinical examination.

Further history revealed that the mother had experienced fever, headache and body aches in the days before and after childbirth. Urine and nasopharyngeal tests performed for respiratory viruses at the maternity ward were negative. The infant's older brother had been home from nursery with mild fever, cough and nasal discharge in the days immediately before and after mother and baby returned from the maternity ward.

Fever in infants under three months is uncommon, and febrile children in this age group should be assessed by a doctor. The infant was lethargic, irritable and reluctant to feed. Such nonspecific symptoms can be early signs of a serious bacterial infection, which it is important to rule out. However, the combination of fever and erythematous pharynx, an older sibling with upper respiratory symptoms, and maternal fever, headache and body aches raised suspicion of a viral infection.

Biochemical tests in the infant showed a CRP of 3.8 mg/L (reference < 5), white blood cell count 15.9 × 10^9/L (9–30 × 10^9/L), neutrophils 8.7 × 10^9/L (3–25 × 10^9/L) and monocytes 2.7 × 10^9/L (0.1–2.0 × 10^9/L). Blood cultures, serum, urine, nasopharyngeal and stool samples were sent for microbiological analysis. Lumbar puncture was attempted but unsuccessful. Given the infant's age and the absence of a clear infectious focus, intravenous antibiotic therapy was initiated with ampicillin 50 mg/kg three times daily and gentamicin 6 mg/kg once daily. The infant was admitted to hospital for further investigation and observation while awaiting test results. During the hospital stay, he developed a fever, with a rectal temperature of 38.6 °C, which responded to paracetamol. He gradually became more lethargic, protested less and showed reduced responsiveness to needle pricks. The infant was exclusively breastfed and did not receive any additional fluid therapy.

Neonatal fever of unknown origin requires in-hospital evaluation. Diagnostic work-up includes blood cultures, urine culture and nasopharyngeal sampling, with a low threshold for lumbar puncture to detect central nervous system

infection.

Sepsis in neonates admitted to hospital from home may be caused by bacteria, such as group B beta-haemolytic streptococci or Gram-negative enteric bacteria. Broad empirical antibiotic therapy is therefore required. Treatment should be adjusted if a microbial pathogen is identified, and discontinued where there is no evidence of bacterial infection.

Empirical antibiotic therapy with gentamicin and ampicillin was initiated in accordance with the guidelines (1). Aciclovir was not administered, as there was no suspicion of central nervous system infection with herpes simplex virus.

After two days in the paediatric ward, the results of the nasopharyngeal, serum and stool samples were ready. PCR analysis of the nasopharyngeal specimen was negative for respiratory syncytial virus, influenza virus, SARS-CoV-2, metapneumovirus, rhinovirus, adenovirus, parainfluenza virus, enterovirus D68, Chlamydia pneumoniae and Mycoplasma pneumoniae. Serum and stool samples were analysed using an in-house PCR method targeting enteroviruses and parechoviruses, and enterovirus was found in both specimens. The infant began to feed better, gained weight and his temperature decreased. As biochemical markers were consistent with a viral infection and there were no clear signs of meningitis, no further attempts at lumbar puncture were made, and antibiotic therapy was discontinued. The infant, now eight days old, was discharged with an open return arrangement to the paediatric emergency department should his general condition deteriorate or in the event of fever.

Enterovirus is a common cause of neonatal infection (2). Older children often have mild or asymptomatic courses, whereas neonates, particularly those less than 30 days old, are at higher risk of severe disease. Hepatitis, meningitis and myocarditis are among the possible manifestations. In addition, enterovirus infection in neonates can cause a sepsis-like illness. Given the high prevalence of enterovirus and the possibility of asymptomatic infection, detection of the virus does not rule out a concomitant bacterial infection. This is particularly the case when enterovirus is found in stool samples. In this infant, the virus was also detected in serum, indicating a symptomatic infection. The biochemical findings supported a viral aetiology of the illness, and antibiotic therapy was therefore discontinued. There is no specific antiviral treatment for enterovirus, and management is symptomatic.

Enterovirus is most frequently transmitted via the faecal–oral route or through droplets or contact with respiratory secretions. Transmission from older siblings, particularly those attending nursery, is a common source of viral infection in neonates. In this patient, transmission from the mother may also have occurred, either before, during or after childbirth.

Two days later, the mother and her now ten-day-old son returned to the paediatric emergency department due to increasing fever and irritability. The infant had slept little, and rectal temperature was 39.0 °C. On examination, he was crying vigorously and exhibited motor agitation. Blood tests showed monocyte counts at the upper end of the reference range, with all other values unremarkable. Blood and urine cultures from the previous admission showed no bacterial growth. The infant was admitted without initiation of antibiotics,

as the infection was still considered viral. The following morning, his fever had decreased to 36.6 °C, and the family was discharged with an open return if symptoms worsened.

The following evening, the mother and son returned to the paediatric emergency department. The infant had experienced repeated episodes of brief, symmetrical jerking of the arms and legs. He was admitted to the paediatric ward, where nurses observed multiple seizures. Initially, he had a series of seizures lasting 2–3 minutes each, with a few seconds in between. These later evolved into jerking episodes of 1–2 minutes' duration occurring approximately once per hour. The seizures were rapid, jerky and occurred while awake, with affected body parts varying from the head to one or more limbs. Transient drops in oxygen saturation were observed during the episodes, reaching a low of 74 % with central cyanosis. Clinical examination and vital signs, including temperature, were otherwise unremarkable.

Blood tests showed Hb 16.3 g/dL (14.0–22.0), leukocytes 12.8 × 10^9/L, monocytes 2.3 × 10^9/L, CRP 1.0 mg/L and glucose 3.8 mmol/L (2.8–4.5). A neurologist recommended lumbar puncture and amplitude-integrated electroencephalography (aEEG), which were performed in the paediatric intensive care unit. Analysis of the cerebrospinal fluid showed leukocytes 180 × 10^6/L (0–30 × 10^6/L), of which 99 % were mononuclear cells, total protein 3.37 g/L (0.20–0.80) and glucose 1.9 mmol/L. The cerebrospinal fluid was also sent for bacterial culture and PCR-based viral testing. In addition, a panel of tests was requested to evaluate for congenital metabolic, autoimmune and genetic conditions. Antiepileptic therapy with intravenous phenobarbital was initiated, first as a loading dose of 20 mg/kg, followed by 2.5 mg/kg twice daily. Intravenous treatment with ampicillin 50 mg/kg three times daily, gentamicin 6 mg/kg once daily and aciclovir 20 mg/kg three times daily was started simultaneously pending microbiological results.

Neonatal seizures can have many causes and may be the first sign of a serious underlying neurological disease in newborns. Treatment is guided by the underlying cause of the seizures. Blood tests should be performed promptly to detect infection, hypoglycaemia, electrolyte disturbances or acid–base imbalances. Lumbar puncture is performed early because central nervous system infection requires rapid treatment. Cerebrospinal fluid can be analysed for microbial agents, autoimmune diseases and metabolic disorders. Imaging is performed to investigate structural causes of seizures, such as haemorrhage, congenital anomalies or thrombi. Testing for rare genetic causes of seizures may also be indicated. Regardless of the aetiology, phenobarbital is the first-line antiepileptic for neonatal seizures (3).

The patient had moderately elevated cerebrospinal fluid cell counts and clinical symptoms consistent with meningoencephalitis. Based on the findings in serum and stool, enterovirus was considered the most likely aetiology, but aciclovir and antibiotics were administered until herpes simplex virus, varicella zoster virus and bacterial causes of meningitis could be ruled out.

Over the following days, the infant remained in hospital for observation and further investigation. aEEG showed series of epileptic activity, corresponding to the clinical seizures. The clinical seizure activity ceased after initiation of phenobarbital. Microbiological analysis of the cerebrospinal fluid showed

enterovirus, but not herpes simplex virus, varicella zoster virus or parechovirus, and there was no bacterial growth. Antibiotic and antiviral therapy were discontinued. MRI of the head showed no pathology.
After five days in hospital, the now three-week-old infant was considered stable and was discharged. At discharge, the phenobarbital dose was adjusted to 4.6 mg/kg/day as a liquid formulation. At follow-up one month later, he had experienced no further seizures. Clinical examination and EEG were unremarkable, and the phenobarbital dose was reduced to 3.5 mg/kg/day. At the three-month follow-up, the infant was considered completely healthy, and phenobarbital was gradually tapered and discontinued. In the meantime, results from the reference laboratory for polio and enterovirus at the Norwegian Institute of Public Health confirmed that the enterovirus found in the infant was coxsackievirus B5. At the two-year follow-up, the child had experienced no further seizures and, based on history and clinical examination, demonstrated normal motor, language and social development.

Discussion

Systemic infections in neonates often present with more nonspecific symptoms and findings than in older children, making diagnosis and evaluation challenging. Clinical presentation in this infant included fluctuating fever, lethargy, reduced feeding and irritability. These can be signs of mild, benign infections, but can also indicate critical illness in infants.

The global mortality rate for neonatal sepsis is estimated at 11–19 % (4). Neonates have an immature immune system, which increases the risk of severe infections. The most common bacterial pathogens are group B streptococci, *Escherichia coli* and staphylococci, but viral agents such as enterovirus, parechovirus and herpes simplex virus can also have a similar clinical picture (5).

Enterovirus is a less well-known, but not uncommon, cause of fever and sepsis-like illness in the neonatal period (6). The virus has several subtypes that can produce a broad spectrum of clinical presentations, depending on the affected organ. In most cases, enterovirus infections are mild and self-limiting. Asymptomatic infection and nonspecific febrile illness are most common. Other manifestations include upper respiratory tract infection, hand–foot–and–mouth disease, meningitis, pericarditis and myocarditis. Viral replication begins in the nasopharynx, followed by a viraemic phase that spreads the virus to various target organs. Final replication occurs in the intestine, hence the name enterovirus (the name does not refer to gastrointestinal symptoms). The most common routes of transmission are faecal–oral and via respiratory secretions. Vertical transmission can also occur in rare cases (2).

The prevalence of different enterovirus subtypes varies over time and by geographic location. In recent years, outbreaks of subtypes causing severe disease in neonates have been reported, including echovirus 11 and coxsackievirus B5. The latter, which was found in our patient, is one of the most common variants (7).

Risk factors for severe disease include prematurity, maternal fever before and during childbirth, and illness in the infant in the days following birth (8). In our case, there were two likely routes of transmission. The patient's mother had fever, nausea and headache immediately before, during and after childbirth. A child in the family who was attending nursery had catarrhal symptoms during the same time period. A nasopharyngeal swab was taken from the mother on the day she gave birth, and was retrospectively analysed for enterovirus with her consent. The analysis revealed enterovirus of the subtype coxsackievirus B5, the same enterovirus type found in the infant. This supports maternal-to-child transmission, which could have occurred in utero, during delivery, through contact with respiratory secretions, or via faecal–oral transmission after birth (2, 9). Detection of the virus in the mother's nasopharyngeal secretions suggests that her infection was in an early phase. Consequently, there had likely been insufficient time for the production of antibodies that could have protected the infant via placental transfer (10).

Enterovirus infection in neonates can be difficult to distinguish from bacterial infections and sepsis. Sepsis is life-threatening and requires prompt treatment with empirical broad-spectrum antibiotics. This case illustrates a situation in which antibiotic therapy was appropriately initiated but could be rapidly discontinued following confirmation of enterovirus. Diagnosis of enterovirus infection in febrile neonates is crucial to avoid unnecessary antibiotic use. In cases of unexplained fever, sepsis or central nervous system infection, sampling of cerebrospinal fluid, blood, stool and, if indicated, nasopharyngeal secretions is recommended to detect enterovirus (11). Parechovirus, which is related to enterovirus and capable of causing similarly severe illness, should also be ruled out.

There is no effective antiviral treatment for enterovirus infections. Intravenous immunoglobulin has shown variable efficacy but can be considered in very severe and life-threatening cases, such as hepatitis, myocarditis and renal failure, where some studies have suggested possible benefit (2). For neonatal seizures, phenobarbital is the first-line therapy, followed by fosphenytoin and levetiracetam (3).

Although enterovirus is the most common cause of meningitis in neonates, knowledge of long-term outcomes is limited. Only a few studies exist, mostly with small cohorts and differing follow-up approaches. Most studies have reported no evidence of sequelae (12–14), and sequelae has been found to be less common after enteroviral meningitis than after bacterial meningitis (12). However, some studies have reported an increased incidence of neurodevelopmental disorders (15–17), which may only become apparent after several years (17). In Norway, there is no standardised long-term follow-up for these patients. More research is needed to determine appropriate follow-up to ensure early identification and intervention for developmental abnormalities.

The patient's parents have consented to publication of the article.

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