CASE REPORT

Recognising early meningitis: a missed opportunity to diagnose meningitis

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SUMMARY

There are ~250 cases of neonatal bacterial meningitis each year in the UK. Clinical evaluation of signs and symptoms of meningitis is challenging, particularly, during the neonatal period. Although uncommon, it is recognised that bacterial meningitis can be present in a child with an apparently normal cerebrospinal fluid (CSF) initially. We report the case of a newborn baby girl who was admitted with concerns regarding 2 dusky episodes. She underwent blood tests, a lumbar puncture and was started on intravenous antibiotics. With negative cultures, normal blood results and following a significant clinical improvement, antibiotics were discontinued after 48 hours and the baby was discharged home. She re-presented to the children's emergency department 7 hours later with a history of an apnoeic episode. A second CSF sample was suggestive of bacterial meningitis. We will discuss the published literature and the potential drawbacks of lumbar punctures and ways to diagnose meningitis early.

BACKGROUND

Over 50% of cases of meningitis occur in children younger than 5 years. The peak incidence is in those younger than 1 year. It is recognised that clinical signs may be lacking in this age group and most clinical guidelines emphasise the importance of screening for meningitis if concerned.

A cerebrospinal fluid (CSF) sample is considered the gold standard test to diagnose and exclude meningitis. A negative cell count on CSF microscopy and negative CSF cultures is reassuring and often leads to discontinuation of intravenous antibiotics. Other parameters, such as the protein and glucose levels, are usually given less attention if the cell count, microscopy and cultures are negative.

This case highlights the importance of analysing lumbar puncture results meticulously, taking presenting symptoms into high consideration and safety netting when lumbar puncture results are negative.

CASE PRESENTATION

A newborn baby girl presented with a history of two dusky episodes at the age of 6 and 11 hours. She was in her mother's arms and responded to simple stimulation. She was the third baby to healthy Caucasian parents with no significant family history and no consanguinity. There were no antenatal and perinatal complications, with no risk factors for sepsis. She was admitted to the neonatal intensive care unit for observation and investigations. Her observations on admission were as follows: heart rate 106 bpm, respiratory rate

35 breaths/min, temperature 36.5°C and an oxygen saturation of 96% in air.

On examination she was felt to be 'quiet' on handling and the rest of the systems examination was unremarkable. There were no other signs or symptoms suggestive of infection. She underwent blood tests, a lumbar puncture and was started on intravenous benzylpenicillin and gentamicin.

Her blood results were within normal range; with a white cell count of $19.9 \times 10^9/L$ and neutrophil count of $13.8 \times 10^9/L$. Her C reactive protein was <2 mg/L. The CSF count was unremarkable; with a red cell count of 280 cells, a polymorph count of 4 cells and lymphocyte count of 1 cell. There were no organisms on microscopy. CSF glucose was 2.3 mmol/L (normal range proportional to blood glucose level at 60–70%, normal range usually is 2.5–4.4 mmol/L) with a corresponding blood glucose level of 3.1 mmol/L and protein level of 0.43 g/L (normal range 0.15–0.45 g/L). A chest X-ray was not performed as there were no respiratory symptoms.

With negative cultures, normal blood results and following a significant clinical improvement, the antibiotics were discontinued after 48 hours and the baby was discharged home.

She re-presented to the children's emergency department 7 hours later with concerns regarding an apnoeic episode. She appeared clinically well and observations were again within normal limits with a heart rate of 108 bpm, temperature of 36.9°C and saturations of 94% in air.

INVESTIGATIONS

On re-presenting she had repeat blood tests and the lumbar puncture was unsuccessful. A chest X-ray was not performed as there were no respiratory signs.

She was started on intravenous cefotaxime and gentamicin. Blood test results showed a white cell count of $10.13 \times 10^9/L$, a neutrophil count of $4.12 \times 10^9/L$ and a CRP of <2 mg/L. A repeat lumbar puncture on the following day was suggestive of bacterial meningitis with a red blood cell count of 270, polymorphs of 304, lymphocytes <1 and no organisms. CSF glucose was 2.2 mmol/L with a corresponding blood glucose level of 4.1 mmol/L and protein level of 2.10 g/L (normal range 0.15–0.45 g/L).

Blood cultures, CSF cultures and the PCR test did not identify the pathogen.

DIFFERENTIAL DIAGNOSIS

She was treated for presumed sepsis during the initial presentation. Negative cell counts, culture

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results and the improving clinical picture were reassuring even though the glucose level was below the lower limit. In retrospect, it is apparent that signs of very early meningitis might have been missed. The spectrum of differential diagnoses on re-presentation was wide and she therefore underwent investigations and management for partially treated meningitis and further blood tests for metabolic conditions.

This neonate had non-specific symptoms and her second lumbar puncture revealed a raised CSF protein level, and CSF glucose of <60% of serum value (~54%). These results are consistent with a diagnosis of congenitally acquired bacterial meningitis. As this was taken following antibiotic treatment it is unsurprising that culture results were negative.

Other differentials that should be considered are: viral meningitis (*Enterovirus*), immune deficiency, parameningeal infection and causes for central, obstructive and mixed apnoea. It is important to consider the possibility that this was iatrogenic meningitis that occurred as a result of the introduction of organisms during the initial lumbar puncture (it was a traumatic tap). Another consideration is that neurological symptoms may occur in the prodromal phase of infection in pathogens such as *Listeria monocytogenes*.

TREATMENT

She had a 14 day course of antibiotics, intravenous cefotaxime and gentamicin, as per the National Institute for Health and Care Excellence guidelines and was discharged home.

OUTCOME AND FOLLOW-UP

The patient remained well throughout her admission and was discharged home after completing the antibiotic course. Her development and health were unremarkable at the follow-up outpatient appointment.

DISCUSSION

Diagnosing neonatal meningitis can be challenging as it cannot be ruled out by clinical examination alone and the interpretation of CSF can be problematic. Classic abnormalities of CSF composition in bacterial meningitis such as pleocytosis, low glucose concentrations, low CSF to blood glucose ratios and high protein levels may be absent in neonates. Low glucose levels and high protein levels alone can be non-specific, in particular, if the lumbar puncture was traumatic as this is known to raise protein levels. This is relevant as approximately one-third of neonatal lumbar punctures are traumatic as reported by Nigrovic *et al.*¹

The following questions need to be addressed: (1) Can a patient have meningitis with a normal CSF? (2) Can a patient without meningitis develop meningitis in the context of a systemic infection? (3) What should we do as clinicians to avoid misdiagnosing a patient with meningitis?

1. How can a patient develop meningitis with a normal CSF? This can occur if the lumbar puncture is performed early in the illness. Kindley and Harris² reported a case with serial lumbar punctures where the initial CSF microscopy and cultures were negative but subsequent lumbar puncture results (27, 28, 70 and 94 hours after the onset of the illness) grew Gram-negative diplococci and showed evidence of polymorphs. It is also recognised that some pathogens can cause neurological symptoms and headaches in the prodromal phase of a meningitic illness without leading to the meningitis phase. Another cause is partially treated meningitis in patients who had antibiotics prior to a lumbar puncture. An additional challenge is that neonatal CSF reference ranges reflect studies with significant limitations such as a small

sample size and inclusion of patients with traumatic lumbar punctures. Garges *et al.*³ conducted a study with 9111 neonates who underwent a lumbar puncture. Ninety-five neonates (1%) had culture proven bacterial meningitis with normal parameters.

2. Can a patient without meningitis develop meningitis in the context of a systemic infection? There is some experimental evidence that this is a possibility. Petersdorf *et al.*⁴ conducted a study where they induced a pneumococcal bacteraemia in dogs. They performed a cisternal puncture in the randomised group but not in the control group. Approximately 60% of the dogs that underwent a cisternal puncture developed meningitis and none in the control group. There was a positive correlation between the incidence of meningitis and the quantity of microorganisms injected into the blood. Another published study⁵ described cases of iatrogenic meningitis where the initial blood cultures were positive and the initial CSF cultures were negative, but repeat lumbar punctures were suggestive of meningitis. They claimed that a perforation of the meninges would increase the risk of developing meningitis. However, this is rare in clinical practice except in ventricular drainages and long traumatic lumbar punctures.
3. What should we do as clinicians to avoid misdiagnosing a patient with meningitis? Clinicians should be guided by the clinical picture, blood cultures and CSF results. Every single CSF parameter should be taken into consideration and not just the cell count and culture. They should treat if in doubt and consider repeating the lumbar puncture. Knight *et al.*⁶ have suggested that a raised lactate, in particular lactate dehydrogenase, might be the key to diagnose very early meningitis. Both parameters are unaffected by traumatic lumbar punctures and superior to glucose and protein levels. Furthermore, CSF lactate has a well-defined reference range and is independent of blood glucose levels. Adenosine deaminase activity has been shown to be a reliable parameter to differentiate between tuberculous and non-tuberculous meningitis in patients with risk factors. It is also advisable to request pneumococcal PCR and virology. Finally, clinicians should keep other causes that mimic meningitis in mind such as parameningeal infection, ear, nose and throat infection, spondylodiscitis and other causes for pleocytosis such as viral (eg, *Enterovirus*) or aseptic meningitis.

To conclude, diagnosing meningitis in neonates requires careful consideration of the clinical presentation, clinical course and investigation results in order to make the best clinical judgments.

Learning points

- ▶ There are drawbacks of using cerebrospinal fluid (CSF) microscopy and biochemistry results alone as a gold standard to exclude meningitis.
- ▶ When interpreting CSF results, the corresponding glucose and protein level are important as they may be suggestive of an early infection.
- ▶ To consider a repeat lumbar puncture if symptoms persist.
- ▶ To carry out further laboratory investigations such as lactate and lactate dehydrogenase as these are unaffected by blood contamination.
- ▶ To give parents appropriate safety netting advice if the initial CSF is negative, as it does not completely exclude meningitis.

Competing interests None declared.

Patient consent Obtained.

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REFERENCES

- 1 Nigrovic LE, Shah SS, Neuman MI. Correction of cerebrospinal fluid protein for the presence of red blood cells in children with a traumatic lumbar puncture. *J Pediatr* 2011;159:158–9.
- 2 Kindley AD, Harris F. Repeat lumbar puncture in the diagnosis of meningitis. *Arch Dis Child* 1978;53:590–2.
- 3 Garges HP, Moody, MA, Cotten CM, *et al.* Neonatal meningitis: what is the correlation among cerebrospinal fluid cultures, blood cultures, and cerebrospinal fluid parameters? *Pediatrics* 2006;117:1094–100.
- 4 Petersdorf RG, Swarner DR, Garcia M. Studies on the pathogenesis of meningitis. II. Development of meningitis during pneumococcal bacteraemia. *J Clin Invest* 1962;41:320–7.
- 5 Fischer GW, Brenz RW, Alden ER, *et al.* Lumbar punctures and meningitis. *Am J Dis Child* 1975;129:590–2.
- 6 Knight JA, Dudek SM, Haymond RE. Early (chemical) diagnosis of bacterial meningitis—cerebrospinal fluid glucose, lactate, and lactate dehydrogenase compared. *Clin Chem* 1981;27:1431–3.

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