CASE REPORT

Confirmed viral meningitis with normal CSF findings

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SUMMARY

An 18-year-old woman presented with a progressively worsening headache, photophobia feverishness and vomiting. Three weeks previously she had returned to the UK from a trip to Peru. At presentation, she had clinical signs of meningism. On admission, blood tests showed a mild lymphopenia, with a normal C reactive protein and white cell count. Chest X-ray and CT of the head were normal. Cerebrospinal fluid (CSF) microscopy was normal. CSF protein and glucose were in the normal range. MRI of the head and cerebral angiography were also normal. Subsequent molecular testing of CSF detected enterovirus RNA by reverse transcriptase PCR. The patient's clinical syndrome correlated with her virological diagnosis and no other cause of her symptoms was found. Her symptoms were self-limiting and improved with supportive management. This case illustrates an important example of viral central nervous system infection presenting clinically as meningitis but with normal CSF microscopy.

BACKGROUND

We present the case of an 18-year-old woman with a history of recent tropical travel who presented with characteristic clinical features of meningitis. However, initial cerebrospinal fluid (CSF) findings including opening pressure, microscopy and biochemistry were normal. Subsequent molecular testing of CSF detected enterovirus RNA by reverse transcriptase PCR (RT-PCR). This case is a fascinating example of how modern molecular diagnostics are changing our clinical understanding of viral illnesses. The case also reinforces the fact that febrile patients who have recently travelled to exotic destinations may not have exotic infections.

CASE PRESENTATION

An 18-year-old student presented to accident and emergency department for the third time in 3 days. She gave a history of gradually increasing frontal headaches that over the past 4 days had become unbearable and associated with fevers and chills. She had vomited once, and had some mild neck pain and photophobia. Three weeks earlier she had returned from Peru, where she had undertaken voluntary work in an orphanage. She had travelled to Lima and a small rural area near Puna. She did not travel to the Amazon. She was up-to-date with pre-travel vaccinations including typhoid, hepatitis A and yellow fever and in keeping with current recommendations for her itinerary, she did not take malaria prophylaxis. She was bitten relentlessly by flying insects, but not ticks and had no history of animal bites or freshwater contact. She was not sexually active. She was well while abroad, other

than a brief episode of diarrhoea. Her travelling companions and her family were all well.

She had no significant medical history, did not take any regular medications and had not taken any new medication recently, and did not smoke or drink. She had not received any antimicrobial therapy prior to her admission.

On examination she appeared unwell. Her vital signs showed a temperature of 37.4°C, blood pressure of 105/70 mm Hg, pulse 100 bpm and oxygen saturation of 100% on air. She had marked photophobia and moderate neck stiffness, but Kernig's sign was negative. She had no rash, and on full examination no other external signs of disease.

Although she described 'feverishness' before admission, lack of temperature above 38°C likely reflects the fact that this was not documented, but her symptoms were consistent with a febrile illness.

INVESTIGATIONS**Relevant blood test results**

- ▶ Initial blood results: haemoglobin 125 g/L, white cell count (WCC) $3.53 \times 10^9/L$ (neutrophils $2.40 \times 10^9/L$, lymphocytes $0.86 \times 10^9/L$, platelets $189 \times 10^9/L$, C reactive protein 14
- ▶ Malaria immunochromatographic test negative, no malarial parasites seen on blood film
- ▶ HIV1 and 2 antibodies negative

CSF results

- ▶ CSF appearance clear and colourless
- ▶ CSF microscopy: WCC $2/mm^3$, red blood cells $21/mm^3$, no organisms seen
- ▶ CSF protein 0.24 g/L, CSF glucose 3.2 mmol/L
- ▶ CSF ferritin 6 ng/mL (normal range <16 ng/mL); no CSF pigments detected; no evidence to suggest intracranial haemorrhage
- ▶ CSF culture: no bacterial growth
- ▶ CSF viral PCR: enterovirus RNA detected; herpes simplex virus (HSV) and varicella zoster virus (VZV) DNA not detected. Results consistent with current enterovirus infection

Microbiology and Virology results

- ▶ Nasopharyngeal aspirate respiratory virus nucleic acid detection negative for enterovirus and the rest of the viral screen in respiratory PCR panel
- ▶ Dengue virus IgM + IgG antibodies negative; dengue virus PCR negative
- ▶ St Louis encephalitis virus IgG (IF) negative
- ▶ Yellow fever virus IgG (IF) negative
- ▶ Eastern equine encephalomyelitis virus IgG (IF) negative
- ▶ Western equine encephalomyelitis virus IgG (IF) negative

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- ▶ Venezuelan equine encephalitis virus IgG (IF) negative
- ▶ West Nile virus IgM and IgG antibody negative

Radiological investigations

- ▶ CXR normal
- ▶ CT of the head on day 1 of admission: normal
- ▶ MRI of the head on day 2 of admission: normal
- ▶ CT of the venogram cerebral on day 2 of admission: no evidence of cerebral venous occlusive disease

DIFFERENTIAL DIAGNOSIS

This case represented a diagnostic dilemma because of the discordance between clinical and initial investigation findings. The clinical features were strongly suggestive of meningitis, most likely of viral or bacterial aetiology, but the initial CSF examination was normal. Central venous thrombosis was therefore considered, and CT angiography was performed and was normal. The diagnosis became apparent on the second day of admission, when enterovirus RNA was detected by RT-PCR in the CSF.

TREATMENT

Despite the clinical diagnosis of meningitis, the patient was not given empirical antimicrobial therapy prior to lumbar puncture because her illness was indolent in onset, she remained generally well and there was minimal delay in undertaking the procedure. The advantage of this strategy is an improved rate of microbiological diagnosis in bacterial meningitis. In view of her normal CSF findings, she was managed supportively with intravenous fluids, analgesia and antiemetics. Management of enterovirus infections, as subsequently confirmed in this case, is also supportive. The patient was nursed in a side-room with standard enteric precautions to prevent transmission.

OUTCOME AND FOLLOW-UP

The patient remained haemodynamically stable, and symptomatically improved during her 4-day admission. At follow-up in the infectious diseases clinic 1 week after discharge, she was well.

DISCUSSION

Enteroviruses are the most common cause of viral meningitis, accounting for the majority of cases of aseptic meningitis where a cause is determined.¹ Enteroviral disease follows a seasonal pattern, the peak incidence being between late summer and autumn.¹ Children are more commonly affected by enteroviral infections than adults, although enterovirus remains a leading cause of viral meningitis in adults along with HSV-2 and VZV.² Enteroviral meningitis is typically characterised by headache, fever, nausea, vomiting, photophobia, neck stiffness and occasionally rash.² It cannot be distinguished from other causes of central nervous system (CNS) infection and therefore a rapid diagnosis is important for appropriate management and infection control.³ Historically the diagnosis was made by culturing CSF in cell lines, but this has been replaced by rapid, more sensitive and highly specific PCR-based molecular assays.⁴ Thus, the diagnosis is now carried out on the basis of clinical and epidemiological features and confirmed by the detection of RNA in the CSF by PCR. Even when viral meningitis is the most likely diagnosis, it is important to establish a viral aetiology early to decrease unnecessary use of antibiotics, the length of hospital stay and the health costs associated with further investigations.

Viral meningitis is generally associated with a raised WCC with a lymphocyte predominance in the CSF.² However, several

recent studies have shown that CSF pleocytosis may not be present in 16–18% of cases of enteroviral meningitis in children.⁵ The absence of a raised WCC in CSF is associated with a younger age of presentation (77% in neonates vs 44% in young infants aged 4–7 weeks).⁶ It is worth considering that Human Parechovirus (HPeV: formerly echovirus 22 and 23) is also an increasingly recognised cause of aseptic meningitis, particularly in children, which can be associated with normal CSF findings.⁷ This should be considered as a differential when suspecting aseptic viral meningitis. In all these studies, the diagnosis of enteroviral meningitis was confirmed by CSF PCR. This phenomenon has also been observed in an adult population. Ihekweba *et al*² found that enteroviruses are the leading cause of viral meningitis in the immunocompetent adult population and observed that the CSF WCC was lower than in meningitis of other viral aetiologies. In 2 of 22 cases of enteroviral meningitis described in the study the reported CSF value was <1 cells/mm³, suggesting that this might be the case in around 10% of cases.

Learning points

- ▶ Normal cerebrospinal fluid (CSF) findings do not exclude viral meningitis.
- ▶ In the appropriate clinical setting, PCR testing of CSF should be performed even on samples with normal cell counts.
- ▶ Rapid return of PCR results could save money on hospital stay, further investigations and avoid unnecessary antibiotic use.
- ▶ It is important to consider common infections that are prevalent worldwide in the differential diagnosis of patients with tropical travel. In travellers, it can help to formulate two differential diagnoses: one taking account of the travel, and one ignoring it.
- ▶ Withholding antibiotics (if the clinical index of suspicion of bacterial meningitis is low) is a key step in antibiotic stewardship, as it increases the likelihood of obtaining a microbiological diagnosis, reduces bacterial resistance and complications of antibiotic overuse.
- ▶ Human Parechovirus (formerly echovirus 22 and 23) is an increasingly recognised cause of aseptic meningitis which can be associated with normal CSF findings. This should be considered as a differential when suspecting aseptic viral meningitis.

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