Novel diagnostic procedure

Clues to diagnosing culture negative *Listeria* rhombencephalitis

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Summary

A previously healthy 35-year-old Caucasian woman developed left body (including facial) hemianaesthesia, asymmetrical lower cranial nerve palsies and cerebellar signs after a 4-day history of headache, nausea and vomiting. Serial blood and cerebrospinal fluid (CSF) cultures returned negative for a culprit organism. CSF examination revealed a lymphocytic pleocytosis and an elevated protein count. CSF cytological examination identified plasma cells. MRI of brain showed multiple ring-enhancing 'abscess-like' lesions in the brainstem and upper cervical cord together with abnormal meningeal enhancement. A decision was made to treat her empirically for *Listeria* rhombencephalitis to which she responded completely. CSF PCR eventually returned positive for *Listeria monocytogenes*. This case illustrates the utility of clinical features, MRI, CSF cytology and PCR in diagnosis and treatment of culture negative *L monocytogenes* rhombencephalitis in an immunocompetent individual.

BACKGROUND

This is an important and educational case as it emphasises the importance of recognising the MRI and clinical findings as manifestations of central nervous system listeriosis, a life-threatening infection. It also highlights the emerging role of cerebrospinal fluid (CSF)-PCR testing for *Listeria*.

CASE PRESENTATION

A previously healthy 35-year-old Caucasian woman presented to the emergency department with left body hemianaesthesia which developed after a 4-day history of headaches, nausea, vomiting and malaise.

The frontal headache which developed on the second day of the illness was devoid of any meningism and resistant to analgesia. Two days later, she was afflicted by a sense of left aural fullness and left facial numbness which subsequently spread in a descending fashion to encompass the whole of the left hemibody within 24 h. In retrospect she admitted to difficulty with balance for the previous 3 days. She denied any fever, double vision, speech or swallowing difficulties or limb weakness. There was no history of migrainous headaches, weight loss, night sweats or recent foreign travel. She was married with two children, one of whom had a diarrhoeal illness 6 days ago. She did not smoke or consume alcohol regularly.

On arrival, she was afebrile, alert and orientated. Higher cortical functions, extraocular movements and visual fields were intact. Limb tone, power and reflexes were normal with no evidence of ankle clonus. Plantar responses were flexor.

Abnormal physical findings included left facial hypoaesthesia, right lower motor neuron facial weakness and left gaze-evoked nystagmus. There was also left hemibody anaesthesia, left upper limb dysmetria, dysidiadochokinesis and gait ataxia. The remainder of her physical examination was unremarkable.

INVESTIGATIONS

Her peripheral white cell count and differential were normal and her inflammatory markers (erythrocyte sedimentation rate and C reactive protein) were not elevated. Pregnancy test was negative. Serologies for autoimmune panel, *Borrelia burgdorferi*, *Treponema pallidum* and HIV I and II returned negative results. Six sets of serial peripheral blood cultures were negative.

Lumbar puncture and CSF examination revealed a lymphocytic pleocytosis with 595 white blood cell (WBC)/mm³ (98% lymphocytes). CSF glucose level was 2.9 mmol/l (serum: 5.4 mmol/l) and protein level was slightly elevated at 0.77 g/l (<0.5). No organisms were visualised on Gram stain but CSF cytology revealed the presence of plasma cells. A repeat lumbar puncture performed 10 days after admission revealed 68 WBC/mm³ and a normal protein of 0.35 g/l.

Cytological examination showed a highly cellular CSF containing lymphocytes, eosinophils, polymorphs, plasma cells and histiocytes, consistent with a reactive inflammatory process.

This and the subsequent CSF culture from day 10 of treatment did not identify a culprit organism.

CSF PCR (day 10): Positive for *Listeria monocytogenes* (delayed result).

TREATMENT

On the basis of clinical features, MRI appearances, CSF parameters and cytological examination, our patient was treated empirically with amoxicillin 2 g six times a day and gentamicin 80 mg intravenous three times a day for 2 weeks, to which she responded well (figures 1–3).

OUTCOME AND FOLLOW-UP

Our patient was discharged after 14 days of treatment with no ataxia or headache but she had minimal paraesthesia on

Figure 1 MRI (day 2): T1 postgadolinium.

the left side of her face. She was reviewed in the outpatient department 2 weeks later and remained well. An interval MRI brain scan performed 1 month later showed complete resolution of initial abnormalities (figure 4).

DISCUSSION

L. monocytogenes rhombencephalitis is typically a biphasic illness starting with a prodrome lasting for 4–5 days followed by an abrupt development of neurological symptoms consisting of asymmetrical cranial nerve palsies, cerebellar and long tract signs.¹ The organism is a Gram-positive, intracellular, facultative anaerobe that is

Figure 3 MRI T2-weighted sagittal view.

thought to enter the brainstem by retrograde axonal transport within the cranial nerves innervating the oropharynx.² Case fatalities are high and long-term unfavourable sequelae are frequent even in treated survivors.^{3 4}

This is a disease entity that usually afflicts the elderly or immunocompromised individuals. Although meningitis and meningoencephalitis predominate in the immunosuppressed, pure rhombencephalitis tend to affect immunocompetent patients, as exemplified in our case.⁵ It is also pertinent to point out that our patient did not possess any markers of a systemic inflammatory response syndrome.

The prospective French encephalitis study of 2007⁶ captured 12 cases of *Listeria* encephalitis, making it the

Figure 2 MRI T2-weighted axial cut.

Figure 4 MRI T2 axial (day 14).

fourth most common form of infectious encephalitis in their report. All except for one of their cases were either elderly or immunocompromised individuals. CSF means protein level and WBC count was determined to be significantly higher than other forms of infectious encephalitis. Otherwise, their study confirms the low yield of blood and CSF cultures (42% and 55%, respectively).

MRI brain scans are universally abnormal in subjects with findings of areas of high signal on T2-weighted sequences. The postgadolinium T1-weighted series typically show ring-enhancing lesions reminiscent of micro-abscesses in the pons, medulla and cerebellar peduncles.^{7 8} Similar lesions have also been reported in the spine.⁹

Given the difficulties isolating the organism with conventional cultures and the bad outcomes of untreated or inappropriate antibiotic treatment, a more rapid and accurate diagnostic method is required. Real-time PCR (RT-PCR) has been shown to be a highly promising diagnostic modality in identifying the presence of the organism in the CSF. The highly conserved and specific *hly* gene proved to be a reliable replication target with no false-negative results shown and the turnaround time for RT-PCR is 2 h.

Furthermore, the sensitivity of the technique allows identification of copy numbers as low as 1×100 CFU/ml.¹⁰ The merits of this method of detection was exemplified in our case where low copies of the *Listeria hly* gene were detected in the CSF from the second lumbar puncture after commencement of antibiotics, although the decision to treat empirically was made prior to confirmation of the organism.

Learning points

- ▶ *Listeria monocytogenes* rhombencephalitis needs to be considered and promptly treated in an immunocompetent individual presenting with asymmetrical cranial nerve palsies, cerebellar dysfunction, long tract signs and typical findings on MRI brain even in the absence of systemic inflammatory response syndrome.
- ▶ Real time-PCR of the *Listeria hly* gene appears to be a highly promising diagnostic tool in terms of accuracy and rapidity.

Competing interests None.

Patient consent Obtained.

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