The Differential Beyond HSV and Limbic Encephalitis

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INTRODUCTION
The differential diagnosis for aseptic meningitis is broad (Figure 1). Patients who present with seizures and temporal lobe changes often have viral (HSV) or limbic encephalitis.

Treatment for viral encephalitis with Aciclovir (ACV) has well documented side effects including acute kidney injury (secondary to tubular crystal deposition and interstitial inflammation) and neurotoxicity presenting with confusion, hallucinations and seizures.

In patients whom microbiological results fail to support a diagnosis of viral encephalitis, the diagnosis and treatment should be re-evaluated.

We present a case which highlights the above points.

CASE SUMMARY*

Day 1-3
- 47 year old male
- Presented with a generalised seizure on a background of behaviour change, unsteadiness, left arm weakness and shaking over the preceding 4 months
- Initial white cell count 19.26 x 10^9/L, Neutrophil count 15.84 x 10^9/L, CRP >1
- CT Head reported as “nil acute”
- CSF sampling - raised protein (1.00g/L), normal glucose (3.4mmol/L, serum 4.3mmol/L), and 4x10^6 white cells (100% lymphocytes)
- CSF Culture and viral PCR negative
- HIV test negative
- Started Aciclovir for suspected viral encephalitis and 3 doses of pulsed Methylprednisolone for possible autoimmune encephalitis
- Motion artefact on initial MRI Head and suggested to repeat Day 7
- MRI Head - “Right temporoparietal enhancement. Differentials include herpes and limbic encephalitis” (Figure 2)
- Seizure free since admission, but on day 7 he went into status epilepticus
- Acute Kidney Injury noted on bloods (Figure 3) and the patient was anuric
- Required intubation and haemofiltration on Intensive Care Unit
- His syphilis serology returned as positive, RPR 1:8, IgM negative
- Referred to Infectious Diseases team. History of penicillin allergy with a rash.
- Started Ceftriaxone
- Stopped Aciclovir as HSV encephalitis unlikely given duration of symptoms preceding hospital admission

Day 7
- MRI Head – “Right temporoparietal enhancement. Differentials include herpes and limbic encephalitis” (Figure 2)
- Seizure free since admission, but on day 7 he went into status epilepticus
- Acute Kidney Injury noted on bloods (Figure 3) and the patient was anuric
- Required intubation and haemofiltration on Intensive Care Unit
- His syphilis serology returned as positive, RPR 1:8, IgM negative
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Day 8-9
- Further seizures whenever moved despite management with Propofol, Loevetinacetam, Sodium Valproate, Phenytoin and Midazolam
- Seizures finally stopped with the addition Sodium Thiopentone

Day 10
- CSF Syphilis Serology positive (Figure 4) confirming Quaternary Syphilis
  - Normal cardiac, skin and genital examination

Subsequently
- No seizure activity on EEG on Day 11
- Exubated on Day 14
- He completed 3 weeks of Ceftriaxone and made a reasonable neurological recovery when reviewed 1 month later
- A repeat MRI and lumbar puncture has been planned 3 months following treatment

DISCUSSION
- His estranged wife later revealed that she was treated for Syphilis when pregnant in 1999. Records show that our patient was also tested at that time, but we were not able to trace results. He had never been treated for syphilis.
- Aciclovir levels were tested whilst having intractable seizures for possible toxicity. These revealed the highest levels of CMMG the reference lab had seen. CMMG is a metabolite of ACV, (9-Carboxymethoxymethylguanine) (Figure 5) and elevated levels have been detected in patients with ACV neurotoxicity. We believe ACV neurotoxicity caused the patients intractable seizures whilst on ITU.
- His wife has claimed to been tested for Syphilis by her GP following the patients discharge
- Neurosyphilis occurs years after initial infection and can mimic many conditions (Figure 6). CSF findings include lymphocytosis, elevated protein and positive RPR.

CONCLUSION
Encephalitis
- Syphilis, “the great mimicker”, can present as a Temporoparietal Encephalitis and should be included in the differential diagnosis of HSV or Limbic encephalitis5,6,7
- Patients with possible encephalitis should be managed in conjunction with an infection specialist

Aciclovir
- When treating with IV Aciclovir, regular monitoring of fluid balance and renal function is mandatory
- Consider neurotoxicity in patients with persistent seizures whilst on ACV treatment, especially in the presence of renal disease
- IV Aciclovir has since been added to our Trust antimicrobial alert system, to help timely capture of such patients

REFERENCES

Neurosyphilis Disorder Symptoms Mimicking
- Meningovascular Arteritis causing ischaemic stroke Stroke
- General Paroxysms of the Insane Personality Change, Psychosis, Seizures, Aryl Robertson Pupil Dementia, Psychosis
- Tabes Dorsalis Loss of dorsal column, causing high stepping gait B12 deficiency, Diabetes
- Gummatous Disease Necrotising Granulomas CNS Tumour

Figure 1. Causes of aseptic meningitis1

Figure 2. Patients T2 weighted (left) and FLAIR (right) MRI Head showing enhancement (white) in the right temporoparietal region

Figure 3. Patients renal function whilst on Aciclovir. He had no renal function measured between Day 1 and 7.

Figure 4. Paired Syphilis serology on the patients blood and CSF samples

Figure 5. Patients ACV and CMMG levels and ACVs metabolic pathway to produce CMMG1