

## 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)<sup>2</sup> and neurotoxicity presenting with confusion, hallucinations and seizures<sup>3</sup>. 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  $19.26 \times 10^9/L$ , Neutrophil count  $15.84 \times 10^9/L$ , 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  **$4 \times 10^9/L$  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 of sample	eGFR	Creatinine (umol/L)
Pre-admission	>90	70
Day 1	>90	78
Day 7 (ITU admission)	10	533

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

### Day 8-9

- Further seizures whenever moved despite management with Propofol, Levetiracetam, 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

Test	Blood	CSF
Syphilis Total Antibody	Positive by EIA	
Syphilis RPR	1:8	1:4
Syphilis TPPA	1:>20480	1:81920

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

### Subsequently

- No seizure activity on EEG on Day 11
- Extubated 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

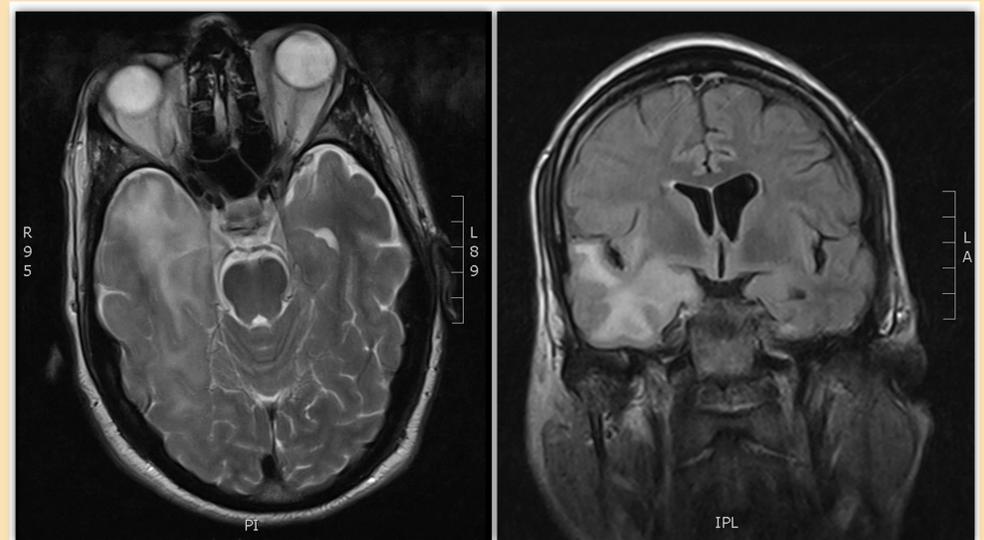
\* Formal consent was obtained from the patient

## 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.

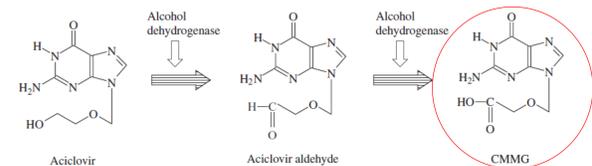
Viral	Parasitic
<ul style="list-style-type: none"> <li>Adenovirus</li> <li>Arboviruses</li> <li>Coxsackieviruses types A and B</li> <li>Cytomegalovirus</li> <li>Echoviruses</li> <li>Encephalomyocarditis virus</li> <li>Epstein-Barr virus</li> <li>Herpes simplex type 1</li> <li>Herpes simplex type 2</li> <li>Human immunodeficiency virus</li> </ul>	<ul style="list-style-type: none"> <li>Angiostrongylus cantonensis</li> <li>Taenia solium (cysticercosis)</li> <li>Toxoplasma gondii</li> <li>Trichinella spiralis</li> </ul>
Bacterial	Drug
<ul style="list-style-type: none"> <li>Actinomyces spp</li> <li>Bacterial endocarditis</li> <li>Borrelia burgdorferi (Lyme disease)</li> <li>Borrelia recurrentis (relapsing fever)</li> <li>Brucella spp</li> <li>Chlamydia spp</li> <li>Leptospira spp</li> <li>Mycobacterium tuberculosis</li> <li>Mycoplasma hominis</li> </ul>	<ul style="list-style-type: none"> <li>Anti-CD3 monoclonal antibody</li> <li>Azathioprine</li> <li>Ibuprofen</li> <li>Other NSAIDs</li> <li>Pyridium (phenazopyridine)</li> <li>Trimethoprim-sulfamethoxazole</li> </ul>
<ul style="list-style-type: none"> <li>Influenza A and B</li> <li>Lymphocytic choriomeningitis virus</li> <li>Measles</li> <li>Mumps</li> <li>Parainfluenza</li> <li>Poliovirus</li> <li>Rotavirus</li> <li>Rubella</li> <li>Vaccinia</li> <li>Varicella-zoster virus</li> </ul>	Malignancy
<ul style="list-style-type: none"> <li>Mycoplasma pneumoniae</li> <li>Nocardia spp</li> <li>Parameningeal bacterial infection (epidural, subdural abscess)</li> <li>Partially treated bacterial meningitis</li> <li>Rickettsia spp</li> <li>Spirillum minor (rat bite fever)</li> <li>Treponema pallidum (syphilis)</li> </ul>	<ul style="list-style-type: none"> <li>Leukemia</li> <li>Lymphoma</li> <li>Metastatic carcinomas and adenocarcinomas</li> </ul>
Fungal	Autoimmune
<ul style="list-style-type: none"> <li>Aspergillus spp</li> <li>Blastomyces dermatitidis</li> <li>Candida spp</li> <li>Coccidioides immitis</li> <li>Cryptococcus neoformans</li> <li>Histoplasma capsulatum</li> <li>Sporothrix schenckii</li> </ul>	<ul style="list-style-type: none"> <li>Behçet's disease</li> <li>Sarcoid</li> <li>Systemic lupus erythematosus</li> <li>Vogt-Koyanagi-Harada syndrome</li> </ul>
	Other
	<ul style="list-style-type: none"> <li>Epidermoid cyst</li> <li>Postvaccination</li> </ul>

**Figure 1.** Causes of aseptic meningitis<sup>1</sup>



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

	ACV Level (mg/L)	CMMG Level (mg/L)
Day 1 (not on ACV)	<0.5	<0.1
Day 7 (ITU admission)	5.7	37.6
Day 9 (2 days after stopping ACV)	<0.5	<0.1



**Figure 5.** Patients ACV and CMMG levels and ACVs metabolic pathway to produce CMMG<sup>3</sup>

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

**Figure 6.** The subtypes of Neurosyphilis and the diseases it can mimic<sup>4</sup>

## CONCLUSION

### Encephalitis

- Syphilis, "the great mimicker", can present as a Temporoparietal Encephalitis and should be included in the differential diagnosis of HSV or Limbic encephalitis<sup>5,6,7</sup>
- 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

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