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Monkeypox encephalitis with transverse myelitis in a female patient

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Abstract:	The 2022 monkeypox outbreak affected over 50 countries around the world, outside of classical endemic areas (1). In July 2022 the outbreak was classified by the World Health Organization as a public health emergency of international concern. The clinical presentation varies from mild to life-changing symptoms, neurological complications are relatively uncommon, and therapeutic interventions for monkeypox disease are limited. We present a case of monkeypox with encephalitis, complicated by transverse myelitis, in a previously fit and well 35-year-old woman, who made a near complete recovery of her neurological symptoms following treatment with tecovirimat, cidofovir, steroids and plasma-exchange. We describe neurological complications associated with orthopoxvirus infections, laboratory diagnostics, the radiological features in this case and discuss treatment options.

Tittle:

Monkeypox encephalitis with transverse myelitis in a ~~Caucasian~~female patient. ~~female~~

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Summary:

The 2022 monkeypox outbreak affected overmore 50 countries around the world, outside of classical endemic areas (1). Since April 2022 the largest outbreak of monkeypox infections outside of classical endemic regions has been reported. In July 2022[1] this the outbreak was classified by the World Health Organizsation as a public health emergency of international concern. The clinical presentation varies from mild to life-changing symptoms, neurological complications are relatively uncommon, andT therapeutic interventions for monkeypox disease are extremely limited. In addition, neurological complications are not common occurrences We present a case of monkeypox with encephalitis, complicated by transverse myelitis, in a previously fit and well 35-year-old woman, who madehad a near complete recovery of her neurological symptomss following responded well to treatment with tecovirimat, cidofovir, steroids and plasma-exchange. We describe neurological complications associated with orthopoxvirus infections, laboratory diagnostics to consider, the radiological features in this caseto help aid diagnosis, and discuss treatment options.

Introduction:

The increase in people Monkeypox cases outside of classical endemic regions was first noted in May 2022. Iinfections were noted in each of the WHO regions, with 88% of laboratory confirmed cases being reported from the European region in the first 2 months of the outbreak (1). Prior to thise recent outbreak, only a minority of cases of monkeypox hadve been observed outside of Africa (2). (2). The current outbreak means that cClinicians around the world need to be familiar with both the common presentation of genital, skin and pharyngeal lesions(3) and the rarer life-threatening complications of this disease such aslike encephalitis.

Monkeypox infections were first recognised in humans in the 1970s. MonkeypoxIt is a zoonotic disease that was originally described in primates; to date but the definitive animal reservoir remains unknown. It is caused by an Orthopox DNA virus. Currently, whole genome sequencing data divides monkeypox species into Clade I (previously the Central African / Congo Basin clade) and Clade II (previously the West Africa clade), responsible for endemic infections in Central and Western Africa respectively. The 2022 outbreak has seen extensive spread outside of endemic countries due to subclade IIb (4). The 2022 outbreak has been demonstrated to disproportionally affect the gay, bisexual and men who have sex with men (GMSM) community. Monkeypox virus infection has an incubation period of 3 to 21 days and is characterised by a prodrome of fever, myalgia and lethargy followed by a characteristic maculopapular rash, and is often a self-limiting illness (3). However, it has been associated with severe disease and prior to the 2022 outbreak carried a 3-6% mortality (1).

Clinicians around the world need to be familiar with both the common presentation of genital, skin and pharyngeal lesions(3) and the rarer life-threatening complications of this disease such as encephalitis.

Neurological complications have previously been documented in relation to ~~seen many with various~~ viral infections of epidemic potential~~us diseases~~, including but not limited to: Sars-CoV-2 (5), MERS-~~COV~~CoV, Zika(6)~~ virus~~, Ebola, smallpox and monkeypox(7). ~~.~~ Encephalopathy, seizures stroke and Guillain-Barre syndrome are all recognised significant but rare complications which increase both morbidity and mortality(7). Three documented cases of encephalitis in the 2022 monkeypox outbreak have been fatal(8). ~~These may present with central nervous and or peripheral nervous signs and symptoms[3]. These complications can increase both morbidity and mortality~~

We discuss a case of a female patient ~~young women~~ with~~, who had~~ monkeypox infection complicated by both encephalitis and transverse myelitis. We highlight the diagnostic tests undertaken, the radiological features seen and our rationale for the treatment options chosen.

Case report:

A 35-year-old ~~UK~~ UK-born white female developed abdominal pain and groin swelling followed the next day by painful vesicular vulval lesions. She reported ~~Her symptoms started five days after~~ unprotected sex with a regular male partner five days before.~~;~~ ~~s~~She had no significant past medical history other than mild gastroesophageal reflux, and no history of underlying immune deficiency. She had ~~no history of~~not been vaccinated against orthopoxviruses. ~~vaccination.~~

On day four of her symptoms, she presented to her local emergency department complaining of a headache. Review was advised in the local sexual health clinic, where she was assessed the ~~following~~ next day. Monkeypox (MPX) was considered as a possible diagnosis; swabs of the lesions were tested for herpes simplex virus (HSV) and~~,~~ varicella zoster virus (VZV), both were negative. ~~(both negative) and~~ MPX~~monkeypox~~ virus polymerase chain reaction (PCR) was positive on the genital lesion swab. (Table 1) ~~(MPX)~~. Her blood-borne virus screen was negative for HIV, Hepatitis B and Hepatitis C.~~,~~ S~~s~~he also tested negative for syphilis. Later that day she was informed by her partner that he had confirmed MPX infection. Due to severe genital pain and problems passing urine, she was admitted to the local Infectious Disease Unit on day six of her illness. She was noted to have MPX lesions at varying stages of evolution on her limbs, hands and trunk. She had extensive, painful lesions on the vulvovaginal area, with local oedema and groin lymphadenopathy. She was managed conservatively with analgesia and oral antibiotics for secondary vulval cellulitis~~infection~~. In addition to her genital and skin swabs, her throat swab was also positive for MPX virus on admission.~~at presentation~~

On day nine of symptoms, she continued to have fever (up to 38.1° C) and became drowsy (Glasgow coma scale (GCS) 14), needing encouragement to take any food or fluids. She continued to have severe genital pain despite escalating analgesia, with new MPX lesions developing on her limbs. After urgent discussion with members of the national MPX multidisciplinary team (MDT), twice daily oral Tecovirimat 600mg was commenced. On day 10, she became drowsier and more confused (GCS 11); encephalitis was suspected therefore a c~~C~~omputerized tomography ~~T~~of ~~h~~head and a lumbar puncture were performed. The lumbar puncture revealed a mild leukocytosis

of 16 x 10^6 white blood cells/μL with normal protein and glucose levels (Table 1). Aciclovir and ceftriaxone treatment were started pending further results.

Bacterial culture and PCR on cerebrospinal fluid (CSF) samples for HSV, VZV and enterovirus were negative. Subsequently, initial orthopoxvirus PCR performed at Colindaleby the UKHSA High Containment Microbiology Laboratory was positive with a cycle threshold (Ct)T value of 36.8. Confirmatory testing was then performed on two extracts from the CSF sample using a monkeypoxvirus specific PCR assay; both were positive with Cts of 34 and 36 respectively. . An MRI head scan showed extensive multifocal areas of abnormal cortical, thalamic and cerebral and cerebellar white matter changes T2 hyperintensities. The distribution of the signal change and cortical thickening was radiologically suggestive of encephalitis. within the brain parenchyma consistent with an encephalitic process. Aciclovir was discontinued, tecovirimat was administered via a nasogastric tube (as the intravenous route formulationiswas not currently available in Europe at the time) until the subject was alert enough to swallow; antibiotics were continued to cover secondary skin infection.

After 10 days of treatment, she remained confused although her GCS had steadily improved (from 8 to 14). She then developed painless urinary retention and the following day (day 19 of illness) was noted to have decreased power (2/5) in both legs throughout all muscle groups. This evolved over 24 hours to flaccid paralysis of both lower limbs with areflexia and absent sensation to all modalities up to the level of T10; upper limb neurology, including reflexes, was normal.

A repeat MRI head scan (on day 20 of illness) revealed diffuse T2/FLAIR hyperintensities within the cerebral periventricular white matter bilaterally, in keeping with a diffuse encephalitis (Figure 1). A whole spine MRI demonstrated multiple central and peripheral intramedullary high T2 signal lesions of varying lengths, with regions of enhancement and associated enhancement of the cauda equina nerve roots (Figure 2). The appearances were considered likely to represent extensive myelitis, with features of cauda equina enhancement. A repeat lumbar puncture demonstrated ongoing lymphocytosis, a mild elevation in protein levels and negative viral (including orthopoxvirus) PCRs (Table 1).

Following discussion at the national MPX MDT and the National Encephalitis MDT, it was felt that the neurological complications of longitudinally extensive transverse myelitis (LETM) were considered to be secondary to a post-infectious immune mediated phenomenon. She had no prior history of central nervous system demyelination or optic neuritis. . but gGiven the presence of ongoing skin lesions and the risks associated with immunosuppression in the context of ongoing infection she was both treated with both mMethylprednisolone (day 22) and a single dose of Cidofovir (on day 24 of illness). Her cognitive function improved over the next five days: mini-Addenbrooke's Cognitive Examination[4] (mini-ACE) was 17/30 initially on day 22, improving to 21/30 on day 26. The power in her lower limbs started to recover to 2/5 in both legs with sensation to light touch returning. The course of tecovirimat was extended to 19 days at which point treatment was discontinued due to abdominal pain (day 28 of illness). On further discussion with the neurology team, the patient was switched to high dose prednisolone (60mg daily) and a 14-day course of plasmapheresis was commenced on day 35 of her illness.

~~At the time of writing~~ Ff~~f~~ollowing seven exchanges, a reducing dose of prednisolone, and a prolonged period of rehabilitation the patient was able to walk independently on her discharge from hospital. She remains well and has~~d~~ recovered from almost all of her neurolog~~y~~ical deficits 3 months after her initial infection.

Table 1. Diagnostic investigations

Day of illness	4	9	17	20	25
CSF:					
WCC, ~~x~~ cells~~10⁶~~/µL		16*		92	
(% lymphocytes)		<1		(100%)	
RBC, cells/µL				<1	
Protein, g/L		0.43		0.82	
CSF/Plasma Glucose, mmol/L		3.4/4.7		3.1/5.5	
Orthopoxvirus PCR (Ct~~T~~ value)		Positive (36.8)		Negative	
Monkeypox virus PCR (Ct value)		Positive (34)			
HSV/VZV/Enterovirus PCR		Negative		Negative	
CMV PCR				Negative	
Lesions:					
Orthopoxvirus PCR (Ct~~T~~ value)	18.7				
Monkeypox virus (Ct~~T~~ value)	16.3				
Throat swab:			Positive		Negative
Orthopoxvirus PCR (Ct~~T~~ value)			(30.4)		
Urine:					Negative
Orthopoxvirus PCR (Ct~~T~~ value)					

* Differential WCC not performed.

Abbreviations: CMV, cytomegalovirus, CSF, cerebrospinal fluid; Ct~~T~~, cycle threshold; HSV, herpes simplex virus; VZV, varicella zoster virus; WCC, white cell count

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Neurological Complications of Epidemic Viral Infections:

To our knowledge this is the first reported case of PCR-confirmed MPX encephalitis complicated by post-infectious LETM ~~transverse myelitis~~ in a woman. There have recently been two cases reported in healthy young ~~gay~~ men (both gay/bisexual/other men who have sex with men) (9).~~.~~ Encephalitis has been reported as part of the current outbreak and remains a serious and sometimes fatal complication (1)(10). Two cases of encephalitis manifested in patients with~~due to~~ proven MPX virus from skin lesions and a report of three in suspected MPX exist in the literature, these have predominantly been in children(10)[,8]~~.~~ ~~Encephalopathy, an a~~Altered mental state was a recognised feature of smallpox with encephalomyelitis documented after both variola virus (smallpox) and Vaccinia virus (post smallpox vaccination) (7)(11–13)[8~~7,9,10~~]. Histological findings of those who have deceased from smallpox and suffered from neurological complications showed acute perivenular demyelination (12). Encephalitis

from smallpox occurred in approximately 1 in 500 patients with variola major and 1 in 2000 individuals with variola minor, presenting 6-10 days into the illness (7,12).

Post-infectious isolated transverse myelitis comprises around 27% of post-infectious central nervous system neurological syndromes, as observed in one previous prospective cohort study (14). Of note, 44% of those patients demonstrated LETM without associated aquaporin-4 antibodies. The majority of cases were steroid responsive. Predictors of poorer outcomes in post-infectious transverse myelitis are greater spinal cord involvement, greater disability at onset and sphincter involvement (14,15). A handful of cases of both transverse myelitis and acute disseminated encephalomyelitis (ADEM) have been reported following smallpox vaccination, however, post-infectious isolated transverse myelitis ~~does not appear to have been previously reported~~ following active MPX infection is a newly described phenomenon (16,17).

Laboratory Diagnostics:

Given the advances in molecular testing, there is increased diagnostic ability to identify the underlying pathogen, as well to monitor treatment. It is recommended that all monkeypox patients have swabs sent from throat and skin lesions for molecular testing(18). ~~-~~If there are concerns of central nervous system ~~CNS~~ involvement then testing of CSF may be informative. A previous case of imported ~~African variant~~ monkeypox, acquired from close contact with Prairie dogs, ~~has~~ had detectable IgM for orthopoxvirus ~~detectable~~ in CSF(19). Our patient underwent two lumbar punctures that showed an evolving lymphocytosis and raised protein levels. The initial sample was positive for monkeypoxvirus~~orthopoxvirus~~ by PCR (Table 1). We therefore hypothesise that this is the first reported case within the current outbreak to link the presence of monkey~~orthopox~~virus in CSF with encephalitis suggesting that there is direct viral invasion of the CSF. ~~In addition to her genital and skin swabs, her throat swab was also positive for MPX at presentation.~~ The second lumbar puncture was negative for monkey~~ortho~~pox virus suggesting that the LETM may be secondary to post-infectious autoimmunity rather than direct viral invasion~~. We believe that this is the first reported case within the current outbreak to link the presence of orthopox virus in CSF with encephalomyelitis suggesting that there is direct viral invasion of the CSF~~.

Other common infectious pathogens known to cause an encephalitic picture should also be considered and tested for in the CSF if clinically relevant, including: Herpes Simplex Virus 1 & 2 (HSV-1/ HSV-2), Varicella Zoster Virus (VZV), Cytomegalovirus (CMV), Epstein- Barr virus, West Nile Virus, Borrelia burgdorferi (Lyme disease), Syphilis , and culture for bacterial, ~~tubercular~~mycobacterial, and fungal pathogens(20).

The analysis of CSF can give clues to the aetiology of the neurological symptoms. Infectious aetiologies are usually associated with raised opening pressures, elevated leucocyte~~wcc~~ counts, lower glucose and raised protein levels, whereas non-infectious causes are associated often associated with normal opening pressures, normal glucose levels and with raised protein levels and leukocyte~~wcc~~ counts(20).

Other markers for other non-infectious causes of myelitis should also be considered. Both Aquaporin-4 and Myelin Oligodendrocyte Glycoprotein antibodies, plus

oligoclonal bands on CSF, were also tested and were negative in our case, as were serum anti-nuclear antibody, extractable nuclear antigen, CSF and serum for paraneoplastic auto-antibodies, and autoantibodies to glial fibrillary acidic protein(20).

Radiological features:

The imaging features seen in this patient with MPX infection differ from those seen in other common viral encephalitisdes. For example, the most common cause of viral encephalitis is HSV, which typically demonstrates involvement of the mesolimbic system, insular cortex and cingulate gyrus, affecting one or both cerebral hemispheres(21). In recent years, there have been several documented cases of Covid-19 encephalitis, where more commonly described findings have included venous sinus thrombosis, grey matter signal changes and micro-haemorrhages(22). Other non-infectious differential diagnoses to consider in our case would include Creutzfeldt-Jakob diseaseCJD, autoimmune encephalitis and hypoxic-ischaemic injury, however the clinical picture and radiology is not typical for these.

In our case the initial MRI examination demonstrated diffuse T2/ fluid attenuated inversion recovery (FLAIR) hyperintensities throughout the cerebral white matter with further hyperintensities within both thalami, the left middle cerebellar peduncle and the brainstem. There was also diffuse T2/FLAIR hyperintensity of the cerebral cortices. The appearances were considered suspicious for an encephalitic process.

At 10 days post-treatment, new signs of areflexia and drop in lower limb power prompted repeat MRI examination. This demonstrated more pronounced T2/FLAIR hyperintense signal change within the cerebral white matter. In addition to the established signal change in the thalami, new hyperintensities within the posterior limb of the left internal capsule, splenium of the corpus callosum were also identified. There was more pronounced diffuse cerebral and new cerebellar cortical swelling with some patchy areas of low apparent diffusion coefficientADC signal implying restricted diffusion (Figure 1). These findings were suggestive of an acute phase of encephalitis. Previously noted lesions within the left middle cerebellar peduncle and brainstem were again evident, however, they had increased in size and now also demonstrated regions of isointense/low ADC signal consistent with reduced diffusivity. There was no evidence of any intracranial pathological contrast enhancement.

Spinal imaging was also performed on this occasion (Figure 2), which displayed long segments of T2/short-tau inversion recovery (STIR) hyperintense signal and cord swelling along the whole length of the spinal cord, involving both grey and white matter tracts. Post-contrast imaging demonstrated patchy foci of enhancement within the cervical spine and avid enhancement of the cauda equina nerve roots. These imaging features were consistent with a longitudinally extensive transverse myelitis (LETM), likely to correspond with the patient's acute deterioration.

Follow-up MR imaging performed nine days later demonstrated reduced cortical swelling, with some modest reduction in the volume of intracranial T2/FLAIR signal change. There was also a reduction in signal change and swelling of the spinal cord, with some improvement in the degree of cord enhancement. Enhancement of the cauda equina nerve roots remained.

Treatment Options:

The optimal antiviral treatment for MPX disease and associated complications is not known, but options include tecovirimat(23)(24), cidofovir, brincidofovir and vaccinia immunoglobulin. The current recommendations for treatment of MPX disease in the UK has recently been published(25). In this patient oral / nasogastric ~~PO/NG~~ T~~t~~ecovirimat was initiated (as intravenous tecovirimat was not available in the UK at the time) when encephalitis was suspected since tecovirimat has been demonstrated to cross the blood brain barrier in animal studies, however human data is still lacking(23). Given the new neurological symptoms in this patient a second antiviral~~,~~ cidofovir _~~,~~ was administered. Whilst cidofovir does not show good penetration of the blood-brain barrier there may be synergy between antivirals(24). Brincidofovir, an oral lipid prodrug of cidofovir, has been shown to be synergistic with ~~tecoviromat~~ tecovirimat in both cell culture and mouse orthopoxvirus models(26), but brincidofovir is not readily available in the UK. These murine studies have shown encouraging findings for the use of tecovirimat and future trials will seek to confirm these in humans. Furthermore, many hospitalised patients have been recruited to observational studies, which will yield more detailed outcome data in due course.

In light of the LETM and significant neurological symptoms experienced by our patient, which were thought to be secondary ~~at least in part~~ to post-infectious autoimmune phenomenon, and g~~G~~iven the poor prognostic markers ~~of our case~~, we proceeded to treat with methylprednisolone and plasmapheresis ~~despite an initial response to corticosteroids~~ as this has previously been shown to be beneficial in acute central nervous system inflammatory demyelinating disease (27). Of note, at her 3 month follow up~~the time of writing~~ plasmapheresis does not appear to have triggered reactivation of MPX infection~~–~~ and may therefore be a safe approach in similar patients~~despite the assumed removal of adaptive antibodies~~.

Conclusion:

Given the tragic outcome of the cases of encephalitis in Spain(1) we wish to highlight the positive outcome in our case with an~~the~~ unusual presentation of neurological sequelae of MPX infection. We believe our patient's care was helped by rapid discussion with appropriate national multi-disciplinary fora and early initiation of anti-viral therapy plus active management of the transverse myelitis.

Future research prospects:

There is a clear and present need for ongoing epidemiological surveillance to ascertain if this outbreak will lead to transmission into novel animal reservoirs allowing it to become endemic outside of Africa. The current treatment options have not been evaluated in human clinical trials and ongoing efforts to evaluate the use of these drugs are underway. Vaccination with Smallpox vaccines has formed an important part of the public health response to date but it remains unclear how efficacious this will prove against monkeypox virus.

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Conflict of interest:

The authors declared no conflicts of interest

Search Strategy and selection criteria:

Data for this Grand Round were identified by searches of PUBMED and references from relevant articles and textbooks. Search terms were “monkeypox”, “encephalitis”, “transverse myelitis” “monkeypox, encephalitis”, “monkeypox, transverse myelitis”, “orthopoxvirus” and “orthopoxvirus, encephalitis”. Only English language papers were reviewed. No date restrictions were set in these searches.

Contributors

JC is the primary author of the article. ~~and~~JC and SC drafted the initial manuscript and conducted the literature searches~~.~~ AJT supervised manuscript planning. JC, SC, and AJT were part of the infectious diseases team that provided direct clinical care to this patient. TP and EH were part of the Neurology team that provided consultation and direct clinical care to this patient. SK and AM reported the patient’s radiological examinations. SA and MA provided local virology input. HC and CG provided virology input from the UKHSA reference lab.

All authors participated in manuscript revision, agreed to submit the manuscript, and approved the final version of the manuscript. All clinical authors had full access to the clinical data.

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Figures:

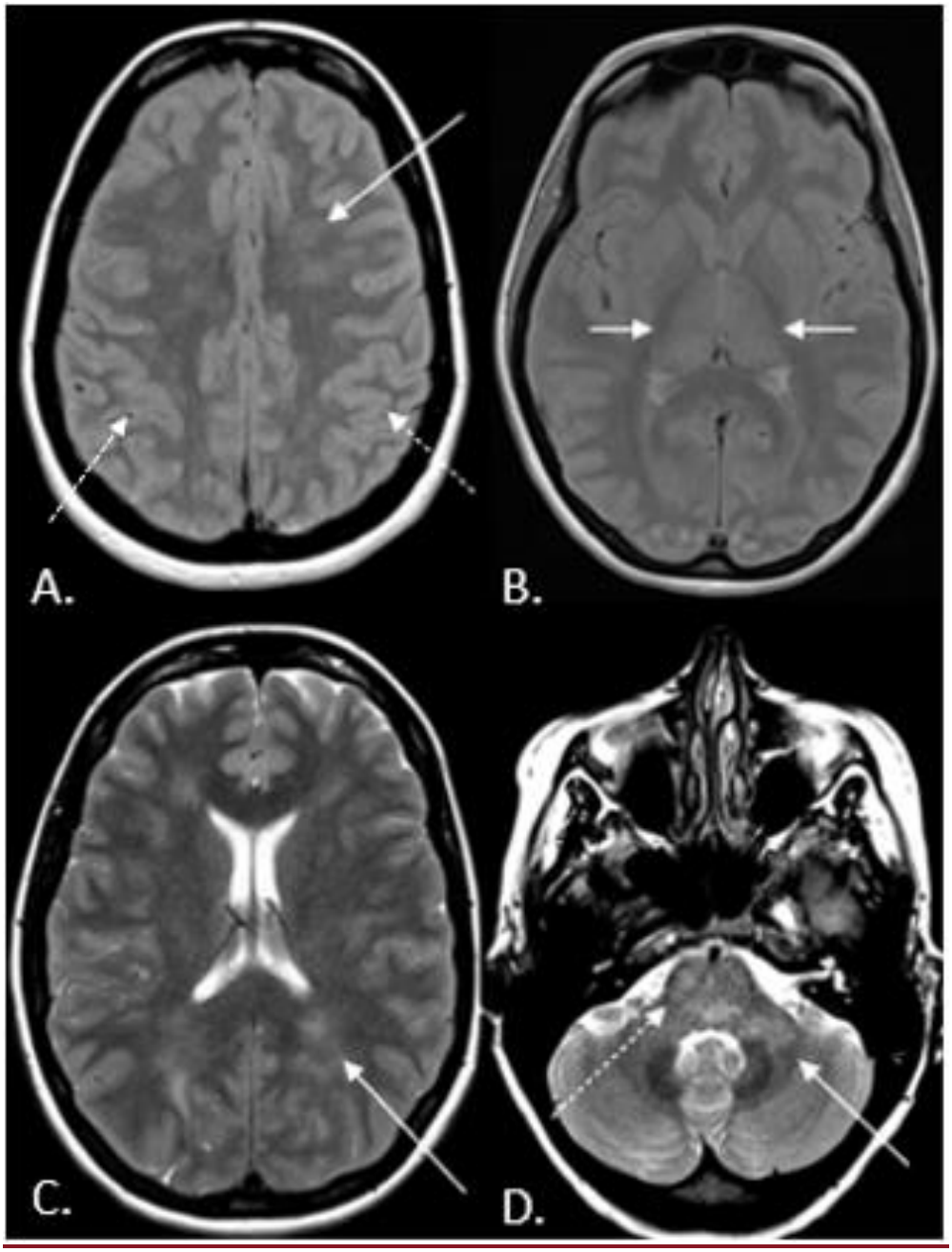

Figure 1: Initial MRI scan. A-B: Axial proton density (PD) images demonstrating supratentorial white matter abnormality (arrow, A) and cortical swelling (dashed arrows, A). More inferiorly, swelling of both thalami was noted (arrows, B). C-D: T2-weighted images demonstrated further hyperintensities within the supratentorial

white matter (arrow, C), middle cerebellar peduncle (arrow, D) and brainstem (dashed arrow, D).

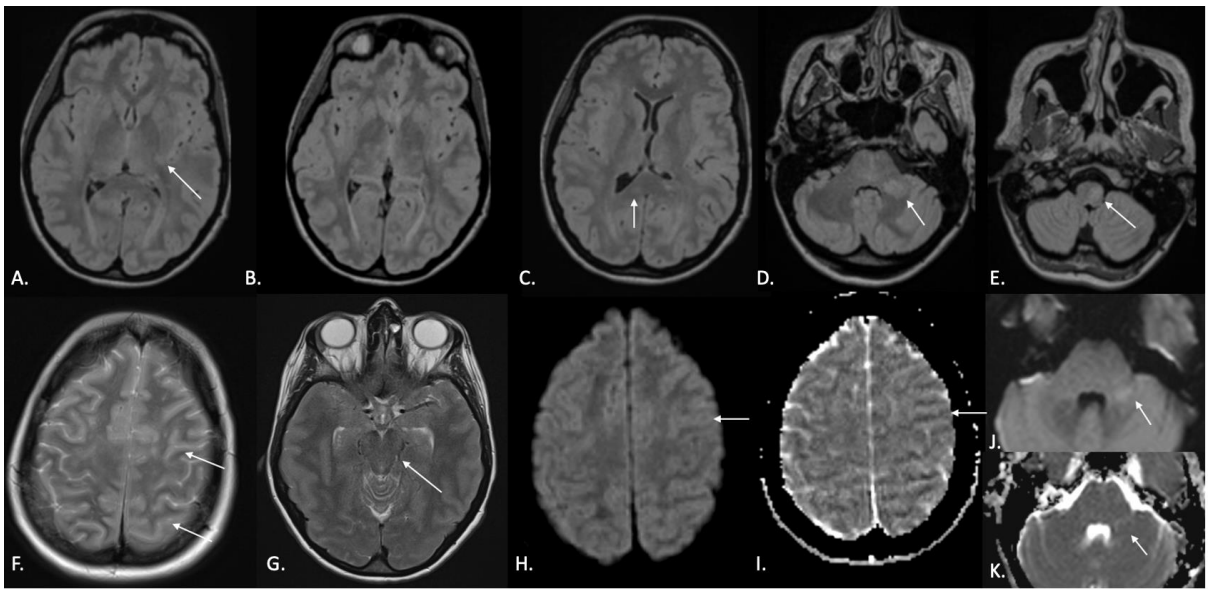

Figure ~~1~~2: Encephalitis changes on MRI head. A-E: Axial 3D-FLAIR images demonstrating abnormal hyperintensity within the posterior limb of the left internal capsule (arrow, A), bilateral thalami (arrow, B), splenium of the corpus callosum (white arrow, C), middle cerebellar peduncle (arrow, D), and left side of the medulla (arrow, E). F-G: Axial T2-sequence highlighting extensive cortical swelling (arrows, Image F) and resulting early uncal herniation with brainstem mass effect (arrow, Image G). H-K: DWI (H and J) and ADC maps (I and K) demonstrate patchy low ADC signal suggesting reduced diffusivity within cerebral cortex (arrows, Images H and I) and the left brachium pontis lesion (arrows Image J and K).

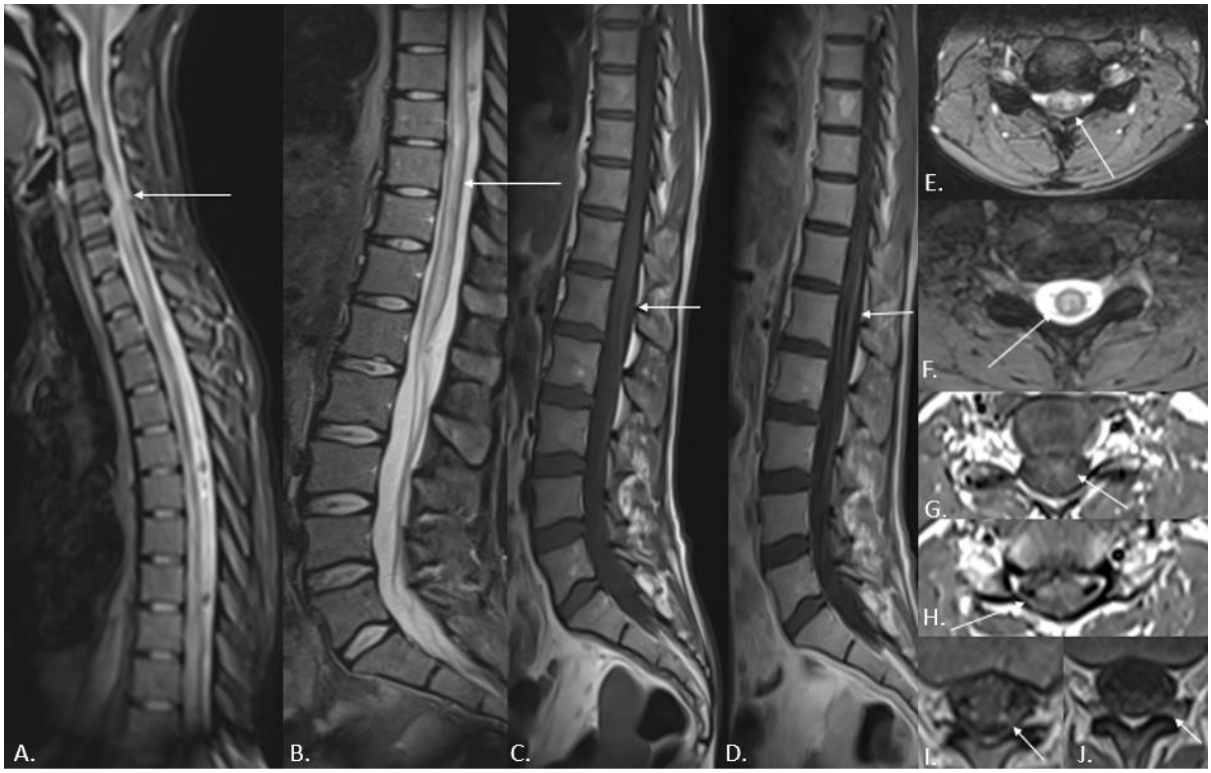

Figure ~~2~~3: Transverse myelitis on MRI spine. A-B: Sagittal STIR sequence showing extensive transverse myelitis of the spinal cord with long segments of T2 hyperintensity and cord swelling in the cervicothoracic (arrow, Image A) and lumbar (arrow, Image B) cord. C-D: Pre and post contrast Sagittal T1 sequences demonstrating avid enhancement of the cauda equina nerve roots. E-F: Axial T2 through the upper and mid cervical spine demonstrating signal hyperintensity involving both the central grey and peripheral white matter (arrows). G-H: Post contrast axial T1 imaging through the upper and mid cervical spine demonstrating patchy enhancement within the cervical spine (arrows). I-J: Axial post contrast T1 imaging through the cauda equina nerve roots demonstrating enhancement of the cauda equina nerve roots.

Tittle:

Monkeypox encephalitis with transverse myelitis in a female patient.

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Summary:

The 2022 monkeypox outbreak affected over 50 countries around the world, outside of classical endemic areas (1). In July 2022 the outbreak was classified by the World Health Organization as a public health emergency of international concern. The clinical presentation varies from mild to life-changing symptoms, neurological complications are relatively uncommon, and therapeutic interventions for monkeypox disease are limited. We present a case of monkeypox with encephalitis, complicated by transverse myelitis, in a previously fit and well 35-year-old woman, who made a near complete recovery of her neurological symptoms following treatment with tecovirimat, cidofovir, steroids and plasma-exchange. We describe neurological complications associated with orthopoxvirus infections, laboratory diagnostics, the radiological features in this case and discuss treatment options.

Introduction:

The increase in people Monkeypox cases outside of classical endemic regions was first noted in May 2022. Infections were noted in each of the WHO regions, with 88% of laboratory confirmed cases being reported from the European region in the first 2 months of the outbreak (1). Prior to this, only a minority of cases of monkeypox had been observed outside of Africa (2).

Monkeypox infections were first recognised in humans in the 1970s. Monkeypox is a zoonotic disease originally described in primates; to date the definitive animal reservoir remains unknown. It is caused by an Orthopox DNA virus. Currently, whole genome sequencing data divides monkeypox species into Clade I (previously the Central African / Congo Basin clade) and Clade II (previously the West Africa clade), responsible for endemic infections in Central and Western Africa respectively. The 2022 outbreak has seen extensive spread outside of endemic countries due to subclade IIb (4). The 2022 outbreak has been demonstrated to disproportionally affect the gay, bisexual and men who have sex with men (GMSM) community. Monkeypox virus infection has an incubation period of 3 to 21 days and is characterised by a prodrome of fever, myalgia and lethargy followed by a characteristic maculopapular rash, and is often a self-limiting illness (3). However, it has been associated with severe disease and prior to the 2022 outbreak carried a 3-6% mortality (1).

Clinicians around the world need to be familiar with both the common presentation of genital, skin and pharyngeal lesions(3) and the rarer life-threatening complications of this disease such as encephalitis.

Neurological complications have previously been documented in relation to many viral infections of epidemic potential, including but not limited to: Sars-CoV-2 (5), MERS-CoV, Zika(6), Ebola, smallpox and monkeypox(7). Encephalopathy, seizures stroke and Guillain-Barre syndrome are all recognised significant but rare complications which increase both morbidity and mortality(7). Three documented cases of encephalitis in the 2022 monkeypox outbreak have been fatal(8).

We discuss a case of a female patient with monkeypox infection complicated by both encephalitis and transverse myelitis. We highlight the diagnostic tests undertaken, the radiological features seen and our rationale for the treatment options chosen.

Case report:

A 35-year-old UK-born white female developed abdominal pain and groin swelling followed the next day by painful vesicular vulval lesions. She reported unprotected sex with a regular male partner five days before. She had no significant past medical history other than mild gastroesophageal reflux, and no history of underlying immune deficiency. She had not been vaccinated against orthopoxviruses.

On day four of her symptoms, she presented to her local emergency department complaining of a headache. Review was advised in the local sexual health clinic, where she was assessed the next day. Monkeypox (MPX) was considered as a possible diagnosis; swabs of the lesions were tested for herpes simplex virus (HSV) and varicella zoster virus (VZV), both were negative. MPX virus polymerase chain reaction (PCR) was positive on the genital lesion swab. (Table 1). Her blood-borne virus screen was negative for HIV, Hepatitis B and Hepatitis C. She also tested negative for syphilis. Later that day she was informed by her partner that he had confirmed MPX infection. Due to severe genital pain and problems passing urine, she was admitted to the local Infectious Disease Unit on day six of her illness. She was noted to have MPX lesions at varying stages of evolution on her limbs, hands and trunk. She had extensive, painful lesions on the vulvovaginal area, with local oedema and groin lymphadenopathy. She was managed conservatively with analgesia and oral antibiotics for secondary vulval cellulitis. In addition to her genital and skin swabs, her throat swab was also positive for MPX virus on admission.

On day nine of symptoms, she continued to have fever (up to 38.1° C) and became drowsy (Glasgow coma scale (GCS) 14), needing encouragement to take any food or fluids. She continued to have severe genital pain despite escalating analgesia, with new MPX lesions developing on her limbs. After urgent discussion with members of the national MPX multidisciplinary team (MDT), twice daily oral Tecovirimat 600mg was commenced. On day 10, she became drowsier and more confused (GCS 11); encephalitis was suspected therefore a computerized tomography ofhead and a lumbar puncture were performed. The lumbar puncture revealed a mild leukocytosis of 16 white blood cells/μL with normal protein and glucose levels (Table 1). Aciclovir and ceftriaxone treatment were started pending further results.

Bacterial culture and PCR on cerebrospinal fluid (CSF) samples for HSV, VZV and enterovirus were negative. Subsequently, initial orthopoxvirus PCR performed by the UKHSA High Containment Microbiology Laboratory was positive with a cycle threshold (Ct) value of 36.8. Confirmatory testing was then performed on two extracts from the CSF sample using a monkeypoxvirus specific PCR assay; both were positive with Cts of 34 and 36 respectively. An MRI head scan showed multifocal areas of abnormal cortical, thalamic and cerebral and cerebellar white matter T2 hyperintensities. The distribution of the signal change and cortical thickening was radiologically suggestive of encephalitis. Aciclovir was discontinued, tecovirimat was administered via a

nasogastric tube (as the intravenous formulationwas not available in Europe at the time) until the subject was alert enough to swallow; antibiotics were continued to cover secondary skin infection.

After 10 days of treatment, she remained confused although her GCS had steadily improved (from 8 to 14). She then developed painless urinary retention and the following day (day 19 of illness) was noted to have decreased power (2/5) in both legs throughout all muscle groups. This evolved over 24 hours to flaccid paralysis of both lower limbs with areflexia and absent sensation to all modalities up to the level of T10; upper limb neurology, including reflexes, was normal.

A repeat MRI head scan (on day 20 of illness) revealed diffuse T2/FLAIR hyperintensities within the cerebral periventricular white matter bilaterally, in keeping with a diffuse encephalitis (Figure 1). A whole spine MRI demonstrated multiple central and peripheral intramedullary high T2 signal lesions of varying lengths, with regions of enhancement and associated enhancement of the cauda equina nerve roots (Figure 2). The appearances were considered likely to represent extensive myelitis, with features of cauda equina enhancement. A repeat lumbar puncture demonstrated ongoing lymphocytosis, a mild elevation in protein levels and negative viral (including orthopoxvirus) PCRs (Table 1).

Following discussion at the national MPX MDT and the National Encephalitis MDT, the neurological complications of longitudinally extensive transverse myelitis (LETM) were considered to be secondary to a post-infectious immune mediated phenomenon. She had no prior history of central nervous system demyelination or optic neuritis. Given the presence of ongoing skin lesions and the risks associated with immunosuppression in the context of ongoing infection she was treated with both methylprednisolone (day 22) and a single dose of Cidofovir (on day 24 of illness). Her cognitive function improved over the next five days: mini-Addenbrooke's Cognitive Examination[4] (mini-ACE) was 17/30 initially on day 22, improving to 21/30 on day 26. The power in her lower limbs started to recover to 2/5 in both legs with sensation to light touch returning. The course of tecovirimat was extended to 19 days at which point treatment was discontinued due to abdominal pain (day 28 of illness). On further discussion with the neurology team, the patient was switched to high dose prednisolone (60mg daily) and a 14-day course of plasmapheresis was commenced on day 35 of her illness.

Following seven exchanges, a reducing dose of prednisolone, and a prolonged period of rehabilitation the patient was able to walk independently on her discharge from hospital. She remains well and had recovered from almost all of her neurological deficits 3 months after her initial infection.

Table 1. Diagnostic investigations

Day of illness	4	9	17	20	25
CSF:					
WCC, cells/μL		16*		92(100%)	
(% lymphocytes)		<1		<1	
RBC, cells/μL					
Protein, g/L		0.43		0.82	
CSF/Plasma Glucose, mmol/L		3.4/4.7		3.1/5.5	
Orthopoxvirus PCR (Ct value)		Positive (36.8)		Negative	
Monkeypox virus (Ct value)		Positive (34)			
HSV/VZV/Enterovirus PCR		Negative		Negative	
CMV PCR				Negative	
Lesions:					
Orthopoxvirus PCR (Ct value)	18.7				
Monkeypox virus (Ct value)	16.3				
Throat swab:			Positive		Negative
Orthopoxvirus PCR (Ct value)			(30.4)		
Urine:					Negative
Orthopoxvirus PCR (Ct value)					

* Differential WCC not performed.

Abbreviations: CMV, cytomegalovirus, CSF, cerebrospinal fluid; Ct, cycle threshold; HSV, herpes simplex virus; VZV, varicella zoster virus; WCC, white cell count

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Neurological Complications of Epidemic Viral Infections:

To our knowledge this is the first reported case of PCR-confirmed MPX encephalitis complicated by post-infectious LETM in a woman. There have recently been two cases reported in healthy young men (both gay/bisexual/other men who have sex with men) (9). Encephalitis has been reported as part of the current outbreak and remains a serious and sometimes fatal complication (1)(10). Two cases of encephalitis manifested in patients with proven MPX virus from skin lesions and a report of three in suspected MPX exist in the literature, these have predominantly been in children(10), Altered mental state was a recognised feature of smallpox with encephalomyelitis documented after both variola virus (smallpox) and Vaccinia virus (post smallpox vaccination) (7)(11–13)[8]. Histological findings of those who have deceased from smallpox and suffered from neurological complications showed acute perivenular demyelination (12). Encephalitis from smallpox occurred in approximately 1 in 500 patients with variola major and 1 in 2000 individuals with variola minor, presenting 6-10 days into the illness (7,12).

Post-infectious isolated transverse myelitis comprises around 27% of post-infectious central nervous system neurological syndromes, as observed in one previous prospective cohort study (14). Of note, 44% of those patients demonstrated LETM without associated aquaporin-4 antibodies. The majority of cases were steroid responsive. Predictors of poorer outcomes in post-infectious transverse myelitis are

greater spinal cord involvement, greater disability at onset and sphincter involvement (14,15). A handful of cases of both transverse myelitis and acute disseminated encephalomyelitis (ADEM) have been reported following smallpox vaccination, however, post-infectious isolated transverse myelitis following active MPX infection is a newly described phenomenon (16,17).

Laboratory Diagnostics:

Given the advances in molecular testing, there is increased diagnostic ability to identify the underlying pathogen, as well to monitor treatment. It is recommended that all monkeypox patients have swabs sent from throat and skin lesions for molecular testing(18). If there are concerns of central nervous system involvement then testing of CSF may be informative. A previous case of imported monkeypox, acquired from close contact with Prairie dogs, had detectable IgM for orthopoxvirus in CSF(19). Our patient underwent two lumbar punctures that showed an evolving lymphocytosis and raised protein levels. The initial sample was positive for monkeypoxvirus by PCR (Table 1). We therefore hypothesise that this is the first reported case within the current outbreak to link the presence of monkeyvirus in CSF with encephalitis suggesting that there is direct viral invasion of the CSF. The second lumbar puncture was negative for monkeypox virus suggesting that the LETM may be secondary to post-infectious autoimmunity rather than direct viral invasion.

Other common infectious pathogens known to cause an encephalitic picture should also be considered and tested for in the CSF if clinically relevant, including: Herpes Simplex Virus 1 & 2 (HSV-1/ HSV-2), Varicella Zoster Virus (VZV), Cytomegalovirus (CMV), Epstein- Barr virus, West Nile Virus, Borrelia burgdorferi (Lyme disease), Syphilis , and culture for bacterial, mycobacterial, and fungal pathogens(20).

The analysis of CSF can give clues to the aetiology of the neurological symptoms. Infectious aetiologies are usually associated with raised opening pressures, elevated leucocyte counts, lower glucose and raised protein levels, whereas non-infectious causes are associated often associated with normal opening pressures, normal glucose levels and with raised protein levels and leukocyte counts(20).

Other markers for other non-infectious causes of myelitis should also be considered. Both Aquaporin-4 and Myelin Oligodendrocyte Glycoprotein antibodies, plus oligoclonal bands on CSF, were also tested and were negative in our case, as were serum anti-nuclear antibody, extractable nuclear antigen, CSF and serum for paraneoplastic auto-antibodies, and autoantibodies to glial fibrillary acidic protein(20).

Radiological features:

The imaging features seen in this patient with MPX infection differ from those seen in other common viral encephalitis. For example, the most common cause of viral encephalitis is HSV, which typically demonstrates involvement of the mesolimbic system, insular cortex and cingulate gyrus, affecting one or both cerebral hemispheres(21). In recent years, there have been several documented cases of Covid-19 encephalitis, where more commonly described findings have included venous sinus thrombosis, grey matter signal changes and micro-haemorrhages(22). Other non-infectious differential diagnoses to consider in our case would include

Creutzfeldt-Jakob disease, autoimmune encephalitis and hypoxic-ischaemic injury, however the clinical picture and radiology is not typical for these.

In our case the initial MRI examination demonstrated diffuse T2 hyperintensities throughout the cerebral white matter with further hyperintensities within both thalami, the left middle cerebellar peduncle and the brainstem. There was also diffuse T2 hyperintensity of the cerebral cortices. The appearances were considered suspicious for an encephalitic process.

At 10 days post-treatment, new signs of areflexia and drop in lower limb power prompted repeat MRI examination. This demonstrated more pronounced T2/FLAIR hyperintense signal change within the cerebral white matter. In addition to the established signal change in the thalami, new hyperintensities within the posterior limb of the left internal capsule, splenium of the corpus callosum were also identified. There was more pronounced diffuse cerebral and new cerebellar cortical swelling with some patchy areas of low apparent diffusion coefficient signal implying restricted diffusion (Figure 1). These findings were suggestive of an acute phase of encephalitis. Previously noted lesions within the left middle cerebellar peduncle and brainstem were again evident, however, they had increased in size and now also demonstrated regions of isointense/low ADC signal consistent with reduced diffusivity. There was no evidence of any intracranial pathological contrast enhancement.

Spinal imaging was also performed on this occasion (Figure 2), which displayed long segments of T2/short-tau inversion recovery (STIR) hyperintense signal and cord swelling along the whole length of the spinal cord, involving both grey and white matter tracts. Post-contrast imaging demonstrated patchy foci of enhancement within the cervical spine and avid enhancement of the cauda equina nerve roots. These imaging features were consistent with a longitudinally extensive transverse myelitis (LETM), likely to correspond with the patient's acute deterioration.

Follow-up MR imaging performed nine days later demonstrated reduced cortical swelling, with some modest reduction in the volume of intracranial T2/FLAIR signal change. There was also a reduction in signal change and swelling of the spinal cord, with some improvement in the degree of cord enhancement. Enhancement of the cauda equina nerve roots remained.

Treatment Options:

The optimal antiviral treatment for MPX disease and associated complications is not known, but options include tecovirimat(23)(24), cidofovir, brincidofovir and vaccinia immunoglobulin. The current recommendations for treatment of MPX disease in the UK has recently been published(25). In this patient oral / nasogastric Tecovirimat was initiated (as intravenous tecovirimat was not available in the UK at the time) when encephalitis was suspected since tecovirimat has been demonstrated to cross the blood brain barrier in animal studies, however human data is still lacking(23). Given the new neurological symptoms in this patient a second antiviral cidofovir was administered. Whilst cidofovir does not show good penetration of the blood-brain barrier there may be synergy between antivirals(24). Brincidofovir, an oral lipid prodrug

of cidofovir, has been shown to be synergistic with tecovirimat in both cell culture and mouse orthopoxvirus models(26), but brincidofovir is not readily available in the UK. These murine studies have shown encouraging findings for the use of tecovirimat and future trials will seek to confirm these in humans. Furthermore, many hospitalised patients have been recruited to observational studies, which will yield more detailed outcome data in due course.

In light of the LETM and significant neurological symptoms experienced by our patient, which were thought to be secondary to post-infectious autoimmune phenomenon, and given the poor prognostic markers, we proceeded to treat with methylprednisolone and plasmapheresis as this has previously been shown to be beneficial in acute central nervous system inflammatory demyelinating disease (27). Of note, at her 3 month follow up plasmapheresis does not appear to have triggered reactivation of MPX infection and may therefore be a safe approach in similar patients.

Conclusion:

Given the tragic outcome of the cases of encephalitis in Spain(1) we wish to highlight the positive outcome in our case with an unusual presentation of neurological sequelae of MPX infection. We believe our patient's care was helped by rapid discussion with appropriate national multi-disciplinary fora and early initiation of anti-viral therapy plus active management of the transverse myelitis.

Future research prospects:

There is a clear and present need for ongoing epidemiological surveillance to ascertain if this outbreak will lead to transmission into novel animal reservoirs allowing it to become endemic outside of Africa. The current treatment options have not been evaluated in human clinical trials and ongoing efforts to evaluate the use of these drugs are underway. Vaccination with Smallpox vaccines has formed an important part of the public health response to date but it remains unclear how efficacious this will prove against monkeypox virus.

Acknowledgement:

We would like to thank the HCID network for invaluable discussions and advice. We also had input from the national encephalitis MDT. We would like to thank Marian Killip from the High Containment Microbiology Laboratory at Colindale who performed thorough PCR work on the CSF sample and Mehmet Yavuz Sheffield Virology Laboratory who performed and developed the local PCR assay. We would like to thank the patient who has provided written informed consent.

Conflict of interest:

The authors declared no conflicts of interest

Search Strategy and selection criteria:

Data for this Grand Round were identified by searches of PUBMED and references from relevant articles and textbooks. Search terms were “monkeypox”, “encephalitis”, “transverse myelitis” “monkeypox, encephalitis”, “monkeypox, transverse myelitis”, “orthopoxvirus” and “orthopoxvirus, encephalitis”. Only English language papers were reviewed. No date restrictions were set in these searches.

Contributors

JC is the primary author of the article. JC and SC drafted the initial manuscript and conducted the literature searches AJT supervised manuscript planning. JC, SC, and AJT were part of the infectious diseases team that provided direct clinical care to this patient. TP and EH were part of the Neurology team that provided consultation and direct clinical care to this patient. SK and AM reported the patient’s radiological examinations. SA and MA provided local virology input. HC and CG provided virology input from the UKHSA reference lab.

All authors participated in manuscript revision, agreed to submit the manuscript, and approved the final version of the manuscript. All clinical authors had full access to the clinical data.

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Figures:

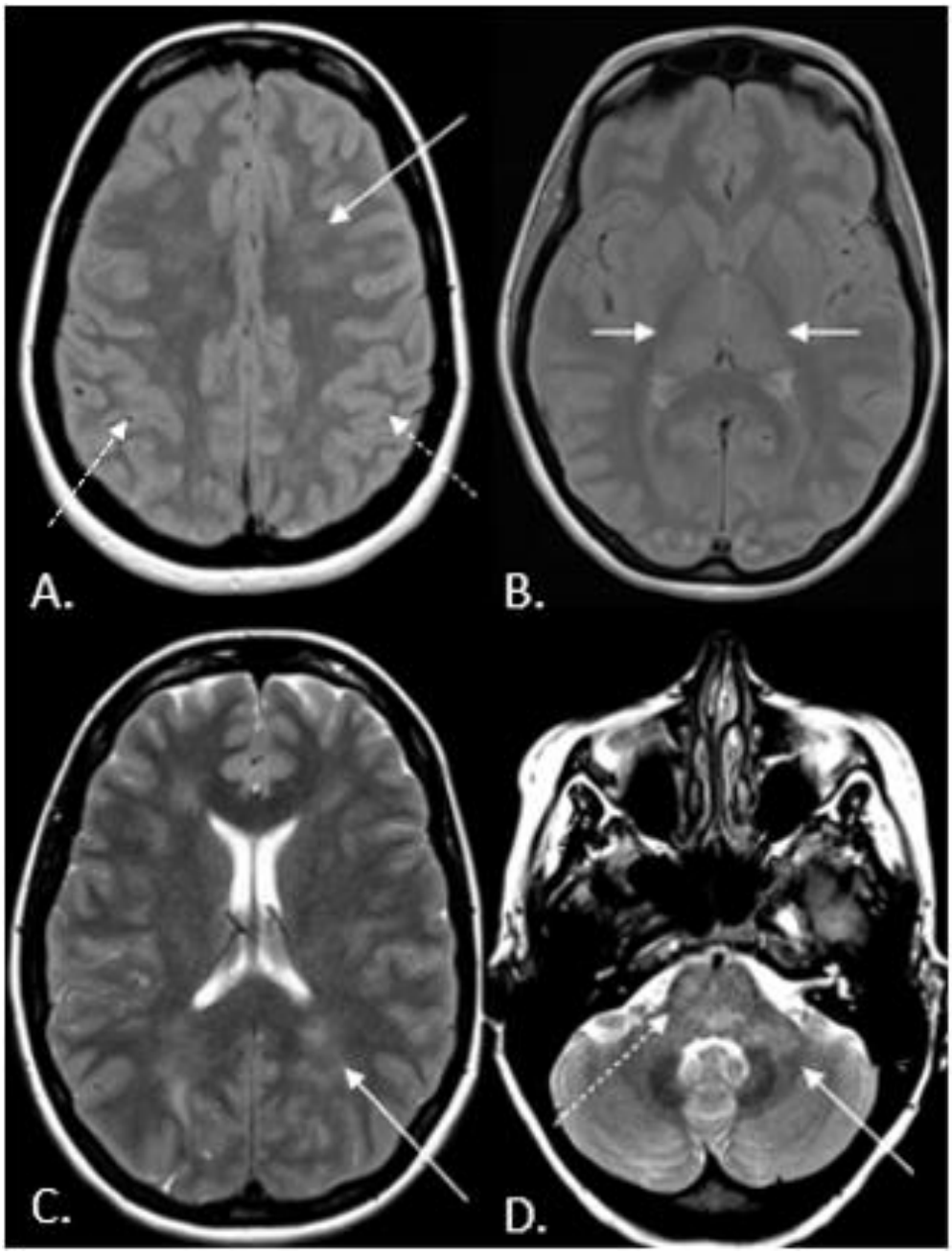

Figure 1: Initial MRI scan. A-B: Axial proton density (PD) images demonstrating supratentorial white matter abnormality (arrow, A) and cortical swelling (dashed arrows, A). More inferiorly, swelling of both thalami was noted (arrows, B). C-D: T2-weighted images demonstrated further hyperintensities within the supratentorial white matter (arrow, C), middle cerebellar peduncle (arrow, D) and brainstem (dashed arrow, D).

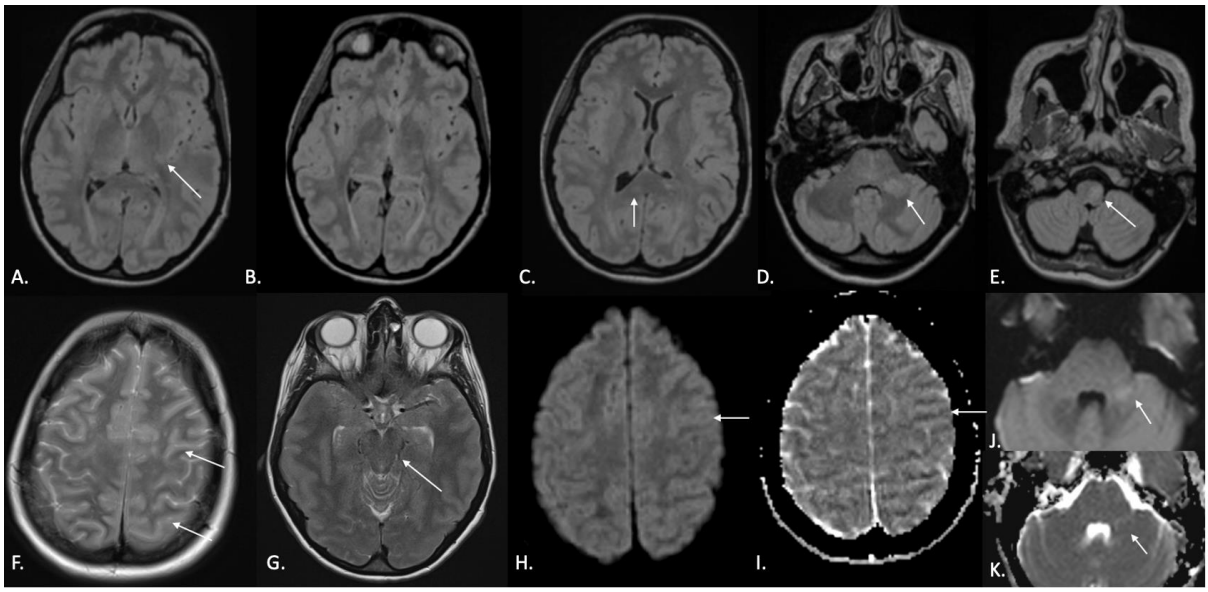

Figure 2: Encephalitis changes on MRI head. A-E: Axial 3D-FLAIR images demonstrating abnormal hyperintensity within the posterior limb of the left internal capsule (arrow, A), bilateral thalami (arrow, B), splenium of the corpus callosum (white arrow, C), middle cerebellar peduncle (arrow, D), and left side of the medulla (arrow, E). F-G: Axial T2-sequence highlighting extensive cortical swelling (arrows, Image F) and resulting early uncal herniation with brainstem mass effect (arrow, Image G). H-K: DWI (H and J) and ADC maps (I and K) demonstrate patchy low ADC signal suggesting reduced diffusivity within cerebral cortex (arrows, Images H and I) and the left brachium pontis lesion (arrows Image J and K).

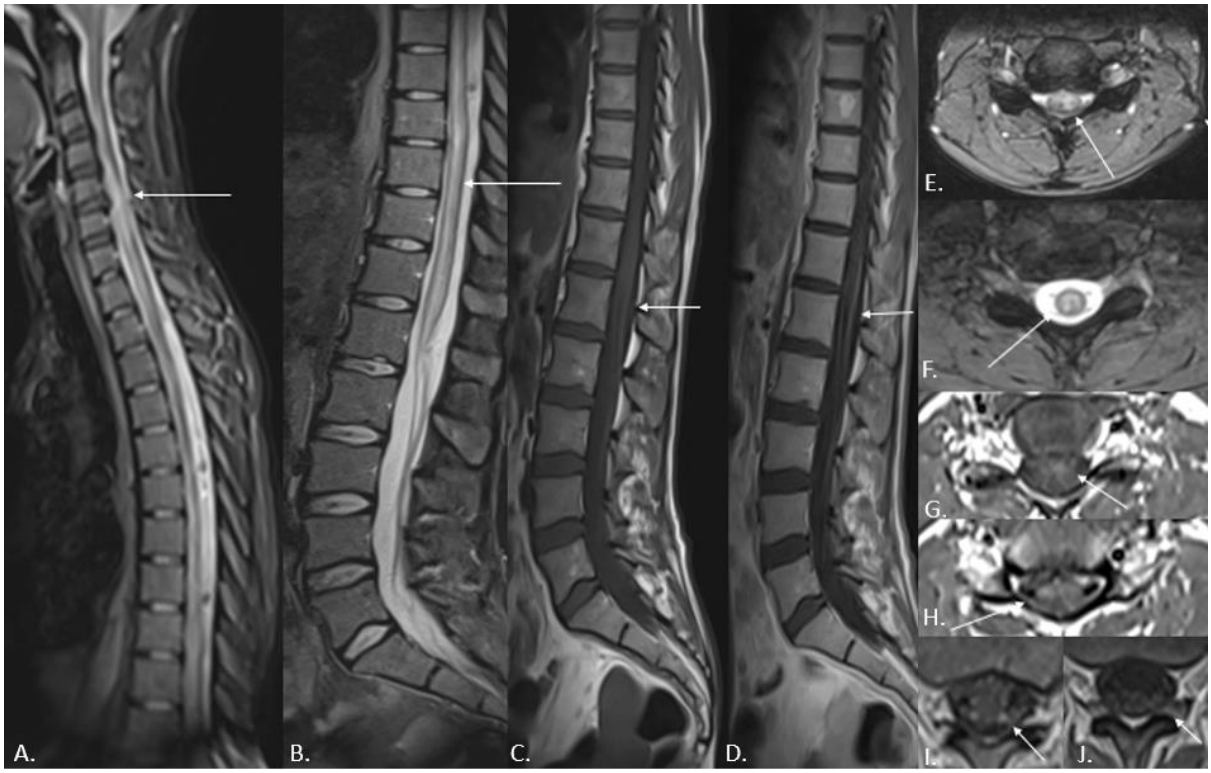

Figure 3: Transverse myelitis on MRI spine. A-B: Sagittal STIR sequence showing extensive transverse myelitis of the spinal cord with long segments of T2 hyperintensity and cord swelling in the cervicothoracic (arrow, Image A) and lumbar (arrow, Image B) cord. C-D: Pre and post contrast Sagittal T1 sequences demonstrating avid enhancement of the cauda equina nerve roots. E-F: Axial T2 through the upper and mid cervical spine demonstrating signal hyperintensity involving both the central grey and peripheral white matter (arrows). G-H: Post contrast axial T1 imaging through the upper and mid cervical spine demonstrating patchy enhancement within the cervical spine (arrows). I-J: Axial post contrast T1 imaging through the cauda equina nerve roots demonstrating enhancement of the cauda equina nerve roots.

Figure

Click here to access/download;Figure;Figure 1.png

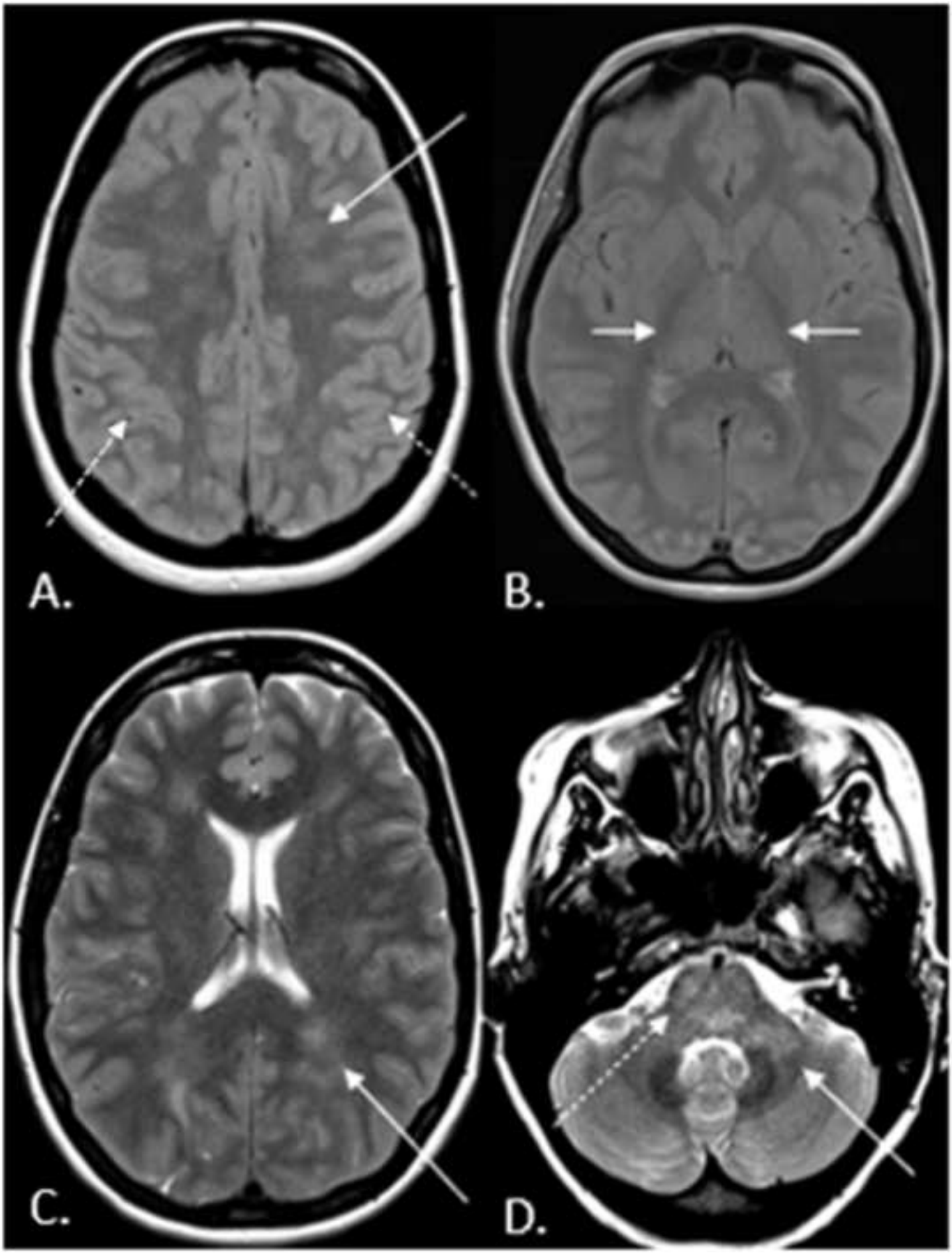

Figure 2

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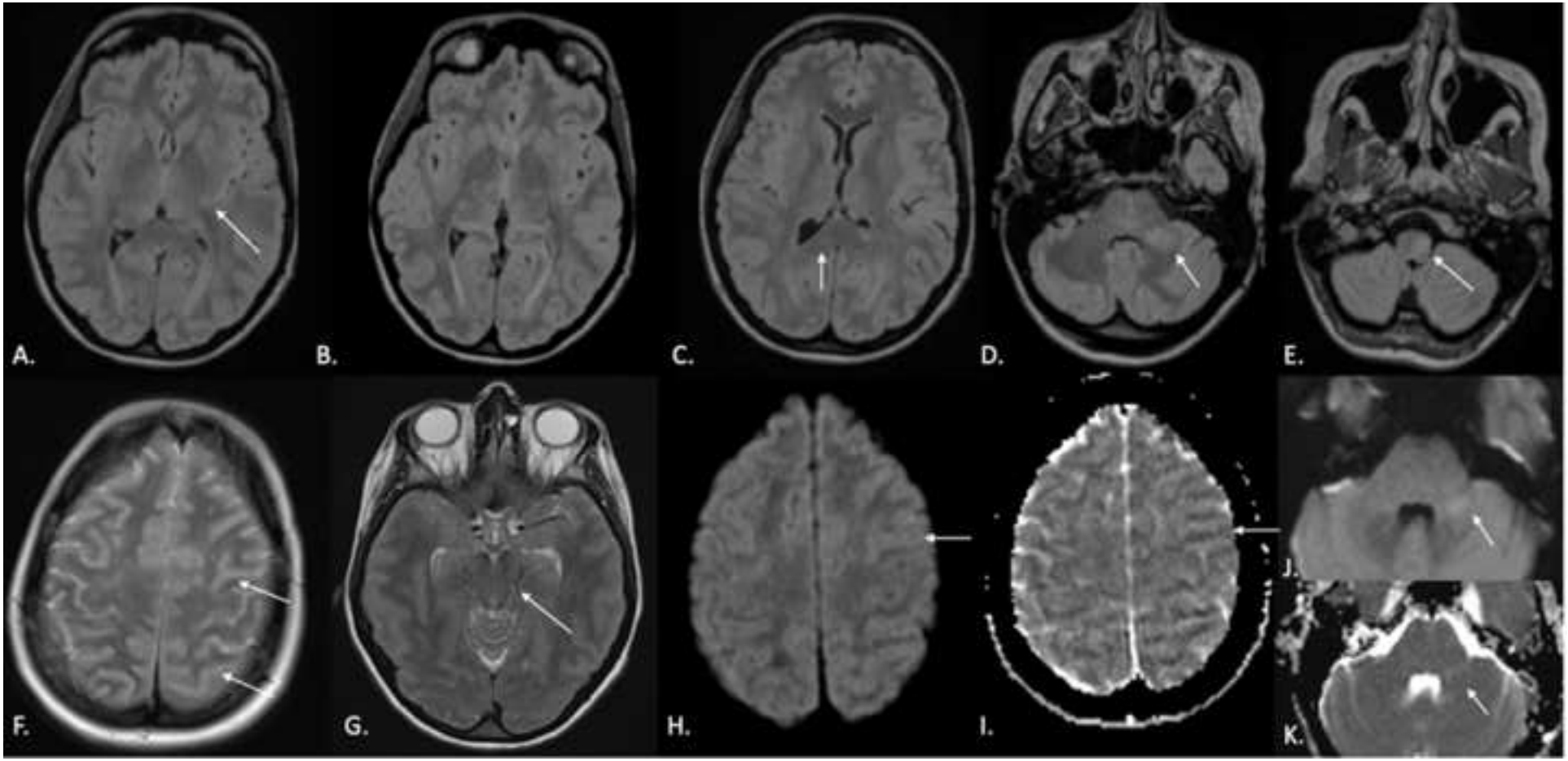

Figure 3

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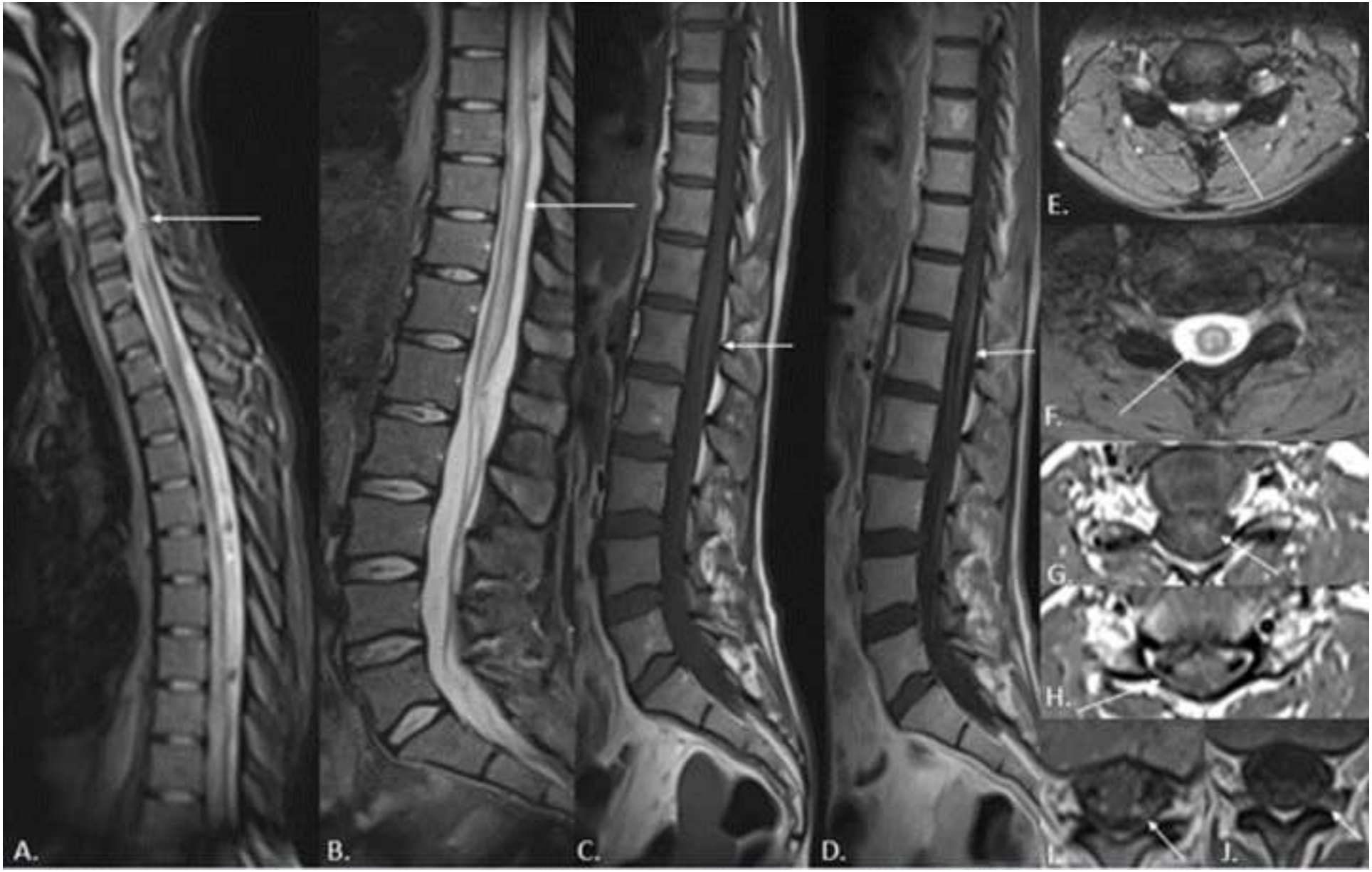

Table

Table 1. Diagnostic investigations

Day of illness	4	9	17	20	25
CSF:					
WCC, cells/μL		16*		92(100%)	
(% lymphocytes)		<1		<1	
RBC, cells/μL					
Protein, g/L		0.43		0.82	
CSF/Plasma Glucose, mmol/L		3.4/4.7		3.1/5.5	
Orthopoxvirus PCR (Ct value)		Positive (36.8)		Negative	
Monkeypoxvirus PCR (Ct value)		Positive (34)			
HSV/VZV/Enterovirus PCR		Negative		Negative	
CMV PCR				Negative	
Lesions:					
Orthopoxvirus PCR (Ct value)	18.7				
Monkeypox virus (Ct value)	16.3				
Throat swab:			Positive		Negative
Orthopoxvirus PCR (Ct value)			(30.4)		
Urine:					Negative
Orthopoxvirus PCR (Ct value)					

* Differential WCC not performed.

Abbreviations: CMV, cytomegalovirus, CSF, cerebrospinal fluid; Ct, cycle threshold; HSV, herpes simplex virus; VZV, varicella zoster virus; WCC, white cell count

Reviewers' comments:

We would like to thank the editors and reviewers for the time and comments which we feel will improve the manuscript and have corrected our manuscript in line with their comments.

Reviewer #1: TITLE
- I would strongly recommend removing "Caucasian" from the title. The implication is that the diagnosis is more common in Africans and under-appreciated in Caucasians, but this is never addressed in the paper and no epidemiological data are presented in this regard. If race is a salient issue, it needs to be discussed. Otherwise, I would advise to delete this and not emphasize it in the title at all.

Response: Thank you for you highlighting this issue. We have amended the tittle to: "**Monkeypox encephalitis with transverse myelitis in a female patient"**

ABSTRACT:
- "responded well to treatment" was vague to my read - which treatment, what is meant by well, when assessed?

Response: In order to remove any ambiguity we have amended the abstract to include the treatments used and the near complete resolution of neurological symptoms.

INTRODUCTION
- I found this lacking detail/precision. The details of the epidemic should be more clear for readers in the future. Also, the list of epidemic viruses is interesting. The virus list should specific that these are of epidemic potential. However, Ebola and smallpox do not present with peripheral nervous system complications. The sentence is not fully accurate as it is.

Response: We have reworded the introduction to clarify points made as above and added references.

CASE
"Her blood-borne virus screen was negative for HIV, Hepatitis B and Hepatitis C, she also tested negative for syphilis."
I would ensure these are two separate sentences.

Response: Thank you for highlighting this we have amended the grammar.

"Subsequently, orthopox PCR performed at Colindale UKHSA reference laboratory was positive with a CT value of 36.8." This is an essential point in the manuscript and ensuing

the details and values are clear with ranges and as much detail as possible is helpful for future cases.

Response: Many thanks for your comment regarding this and we agree it is an important one. The orthopox PCR was validated for monitoring of confirmed Monkeypox cases at Colindale UKHSA High Containment Microbiology reference laboratory. They subsequently performed the Monkeypox specific assay (initially this was reserved for the initial diagnostic samples) on further extracts from the same sample to confirm. The details have been added to the manuscript.

Did the CSF have RBC tested? Xanthochromia present?

Response: The CSF red cell count was less than 1.10^6/L. Xanthochromia was not performed.

When I read: "An MRI head scan showed extensive changes within the brain parenchyma consistent with an encephalitic process." I was expecting to see something more dramatic than what the imaging showed. Perhaps a more precise description of the MRI findings would be better. The MRI brain findings seemed to show edema, minor white matter changes.

Response: Many thanks. We have reworded the manuscript as follows ‘An MRI head scan showed multifocal areas of abnormal cortical, thalamic and cerebral and cerebellar white matter T2 hyperintensities. The distribution of the signal change and cortical thickening was radiologically suggestive of encephalitis.’ In addition, we have included a new figure including the initial MRI scan.

The diagnosis of encephalitis is often considered to include fever, mental status changes, and seizures. Although this definition is not universal, the patient's body temperature is not mentioned and no mention of an EEG or absence of seizures is made.

Response: Our patient had altered mental status, and a temperature of 38.1 at the beginning of her illness. We have added the value in but as she did not have any witnessed seizures nor did she undergo an EEG we have not added this to the text for brevity.

When the authors write " at the time of writing" it is not fully clear when that is and should be more clear for a publication.

Response: In order to clarify the text we have removed the section “at the time of writing” and added the sentence: “She remains well and has recovered almost all of her neurology 3 months after her initial infection.”

Sometimes encephalopathy and encephalitis are used interchangeably (or perhaps on purpose) as in the smallpox history section, but the differences to readers may not be clear.

Response: In order to add clarity to the text we have removed the reference to encephalopathy and replaced it with “an altered mental state”

Similarly, the diagnosis of transverse myelitis in this case is better characterized as an LETM (longitudinally extensive transverse myelitis) throughout based on my interpretation of the images.

Response: Thank you for your comment, we have modified the text and replace transverse myelitis with LETM when referring to our patient’s case.

African variant is mentioned once near the end of the manuscript and is not mentioned before. This would be useful in the background or earlier on.

Response: We have amended the line to clarify that this was a case of monkeypox secondary to contact with infected prairie dogs.

The most controversial part of the discussion is: "To our knowledge this is the first reported case of MPX encephalitis complicated by post-infectious transverse myelitis in a woman." and "We believe that this is the first reported case within the current outbreak to link the presence of orthopox virus in CSF with encephalomyelitis suggesting that there is direct viral invasion of the CSF."

Response: Thank you for your observation, we have amended the discussion to temper our conclusions in line with the comments of the reviewers.

Are the authors postulating the monkeypox virus is the cause of the encephalitis directly even though it was not identified intrathecally in the CSF? This is not proven and should not clear that it is the hypothesis and seems likely. The statements above are inconsistent. The LETM may be post-infectious autoimmunity. The significant improvement from flaccid paralysis to walking after plasma exchange implies an autoimmune process, likely post-infectious. Or do they posit that the myelitis is also viral invasion? They seem to suggest both. The caudal equine nerve root enhancement can also imply an AIDP component given the flaccid paralysis and areflexia. Were nerve

conduction studies performed?

Response: We apologise for the confusion caused, we have sought to clarify the discussion. We hypothesise that there is direct invasion of the CSF by monkeypox virus as our patient's CSF was orthopox and monkeypox virus PCR positive on her initial analysis. We have tempered our discussion to reflect that the LETM may be due to infection or inflammatory changes as we treated both. Nerve conduction studies were not performed.

Plasma exchange does not usually trigger viral disease again to my knowledge. The finding that the patient improved posted PLEX is valuable but I wouldn't have suspected worsening viral disease.
The case and treatment course are interesting. Given the single case, some conclusions should likely be tempered.

Response: Thank you for your comments, In line with your suggestions, we have tempered our conclusions.

Reviewer #2: I have reviewed a manuscript entitled "Monkeypox encephalitis with transverse myelitis in Caucasian female". The manuscript is well written and I feel well informed on the subject having reviewed it.

Minor:

- Please add the future research prospects in this field.
- Please correct "20221" to "2022" in abstract part.

Response: We have corrected the year and amended the reference.

Reviewer #3: This is an interesting case report of a patient with monkeypox virus infection and encephalomyelitis. The case is presented in good detail and the patient was extensively investigated for any other aetiologies and treated with antiviral and immunotherapies with a good response.
1. Did the patient have any underlying immune conditions that could predispose her to CNS manifestations

Response: Our patient was previously fit and well with only gastroesophageal reflux as her past medical history.

2. Genetic testing for primary immune disorders should be considered

Response: Our patient had no significant past medical history of recurrent infections in her preceding 35 years making primary immune disorder unlikely. Genetic testing is not routinely carried out in the UK.

3. What CT value is considered negative. Most labs would consider a CT of 36.8 as borderline or negative.

Response: Many thanks. The CSF was tested twice using the Orthopox assay in which cycles up to 38 with a good exponential curve would be interpreted as positive based on the assay specific parameters developed during PCR validation. This is fairly common practice in UK labs experienced in PCR interpretation. The CSF was tested twice with the same result in the Orthopox assay, and confirmatory testing performed using a monkeypox specific assay which gave CTs of 34 and 36. We have included the lower value in the table for clarity. Lower Cts are expected for the species specific assay so this is in keeping with the orthopox results.

4. In the discussion I would suggest including some limitations. One cannot be certain that this is a viral encephalitis. It could just be ADEM triggered by an infection. The clinical course MRI and CSF findings and response to immunotherapy would be consistent with that possibility. Neurotropism of orthopox viruses has yet to be convincingly demonstrated.

Response: Thank you for your comments, we have tempered our conclusion in line with the previous reviewers comments. We do believe however, that the positive orthopox/monkeypox PCR in CSF lends credence to the neurotropism of monkeypox virus and that this may be the cause of the encephalitis, which was the opinion of the national encephalitis MDT. We concede that the LETM may be more likely to be secondary to post-infectious / immune mediated changes and have changed the discussion in line with this.

5. Another recent review article in JAMA neurology (Billioux et al.) compares the neurological manifestations of the orthopox viruses that may aid in the discussion of these syndromes.

Response: Thank you for highlighting this reference we have added it to our discussion on smallpox vaccine associated encephalitis

Reviewer #4: In this manuscript, Cole et al report a case of encephalomyelitis associated with monkeypox infection. The patient was a previously healthy Caucasian female of 35-year-old who developed an ongoing neurological condition of acute monkeypox infection. She improved after treatment with antiviral drugs, high dose prednisolone and plasmapheresis.
This is an original and interesting report. However, some aspects can be improved. The

references need to be reviewed

Major
1.Introduction - needs a better discussion of current studies and concepts, including epidemiological aspects, in addition to a review of references:
- Example page 3- third paragraph "Neurological complications are seen with various viral infectious diseases, including but not limited to: Sars-CoV-2, MERS-COV, Zika virus, Ebola, smallpox and monkeypox (REFERENCE???). may present with central nervous and or peripheral nervous signs and symptoms3." The reference 3 is about monkeypox.

Response: We have reworded the introduction and added references including one which was not published at the time of the 1st draft of this paper.

2. Methods
There is no mention of approval by the ethics committee and signing the consent form by the patient.

Response: Thank you for highlighting our omission. We do have written informed consent from the patient. As this was merely a descriptive observation of a clinical case and no extra samples were taken and the patient was not enrolled into a research study, formal ethics approval is not typically required nor sought.

2. Discussion.
As the patient presents a neurological picture of acute encephalomyelitis with probable infectious origin (inflammatory CSF characterized by pleocytosis and hyperproteinorrhaquia with positive monkeypox) and not post-infectious. It would be important to justify the use of methylpredisolone and plasmapheresis, considering the use of immunosuppressive drugs and the possibility of spreading of the infection. This is an important issue, since the manuscript may be used as a reference for conduct for many physicians in the world.

Response: We agree that the use of methylprednisolone in the context of infection is not without risk. We have modified our discussion around the use of methylprednisolone to treat the immune mediated phenomenon and commented about the added cidofovir as secondary cover for infection in addition to the tecovirimat.

It would be of fundamental importance to discuss the differential diagnosis of infectious and post-infectious neurological conditions through the CSF exam.

Response: We have added a section describing the expected findings in CSF analysis and reference to a review article discussing this at length.

Minor
There are some grammatical spellers and typing errors in the abstract
- "World Health Organisation" or World Health Organization

Response: We have corrected our spelling mistakes.

Reviewer #5: The authors have described a challenging case of MPXV infection, with an unusual complication that deserves to be published. The “grand round” format adds relevant value for clinicians attending these patients, including useful information. To improve some aspects of the article, I suggest some minor modifications.

MAJOR COMMENTS:
2nd page, Case report, 4th paragraph: could you add some images from the first brain MRI, and describe further the “extensive changes within the brain parenchyma consistent with an encephalitic process”?

Response: A new figure of the initial MRI has been added with further explanatory text.

3rd page, 2nd paragraph: Could you describe why a post-infectious (presumably autoimmune process) transverse myelitis was suspected and not a direct viral neuroinvasion? That statement differs from what you have stated in a later paragraph ("We believe that this is the first reported case within the current outbreak to link the presence of orthopox virus in CSF with encephalomyelitis suggesting that there is direct viral invasion of the CSF").

Response: We have reworded the later section in line with other reviewers comments to suggest that the neuroinvasion may have resulted in encephalitis but that the LETM likely results from a post infectious immune phenomenon.

MINOR COMMENTS:
Summary: Consider changing orthopox to orthopoxvirus throughout the text.

Response: We have amended the text to orthopoxvirus as suggested.

1st page, Case report, 1st paragraph: consider adding orthopoxvirus vaccination status of the reported case.

Response: We have added the patient's lack of orthopoxvirus vaccination.

1st page, Case report, 2nd paragraph: consider writing "MPX virus" or "MPXV": "varicella zoster virus (VZV) (both negative) and monkeypox (MPX) virus". The same in the conclusion (MPXV infection).

Response: We have amended the text in the introduction and conclusion to MPX virus.

2nd page, Case report, 2nd paragraph: since antibiotic therapy is not routinely recommended for MPX, could you describe the rationale for prescribing them? I guess it was due to suspected bacterial superinfection, but it might be clarified.

Response: We have added that she did indeed have secondary bacterial infection causing vulval cellulitis.

2nd page, Case report, 2nd paragraph: MPXV PCR result in skin lesions is not clearly reported in the text.

Response: We have clarified the text by adding "PCR" to the paragraph and referencing the table listing the PCR results.

2nd page, Case report, 3rd paragraph (and table 1): As white blood cells in CSF are more frequently reported as cells/µL, I propose to change the units (16 cells/µL).

Response: We have amended the text and table to reflect new scale.

2nd page, Case report, 4th paragraph: spell the following words the first time in the text: PCR, MRI, Ct, CNS, CSF, ADC, PO, NG, CJD

Response: We have defined all abbreviations at first use and removed superfluous ones.

2nd page, Case report, 4th paragraph: modify CT to Ct throughout the text and the table.

Response: We have modified the text in line with your recommendations.

2nd page, Case report, 4th paragraph: I guess tecovirimat was administered via a nasogastric tube because intravenous tecovirimat is not available in your center. This is

the current situation in Europe. It could be specified (e.g.: "administered via a nasogastric tube as the intravenous route is not currently available in Europe")

Response: Indeed the IV formulation was not available at the time, we have modified the text to include your suggested text.

2nd page, Case report, 7th paragraph: Could you add the dose of systemic steroids?

Response: We have added the dose in the text.

3rd page, 2nd paragraph: "Two cases of encephalitis due to proven MPX and a report of three in suspected MPX exist in the literature, these have predominantly been in children6". I suppose the authors are referring to cases with MPXV isolation in CSF; this could be specified

Response: We have clarified this in the text and updated our reference to reflect this.

4th page, 2nd paragraph: Was MPXV PCR performed in CSF, in addition to orthopoxvirus PCR? If performed and negative result (if so, include that result in the table), could orthopoxvirus PCR have a higher sensitivity than MPXV PCR in CSF, as MPXV PCR has been negative in those recent cases with encephalomyelitis cited in the article?

Response: Many thanks for your comment regarding this. The details of the monkeypox confirmatory testing have been added to the paper.

4th page, 2nd paragraph: consider modifying "African variant monkeypox", as it does not sound fully correct.

Response: We have altered the text to imported monkeypox acquired through close contact with Prairie dogs. To more accurately distinguish this method of transmission from our case.

4th page, 2nd paragraph: Consider moving "In addition to her genital and skin swabs, her throat swab was also positive for MPX at presentation" to the Case report section

Response: We have moved the throat swab and skin lesion results to the case report section.

4th page, 3rd paragraph: change "tubercular" to "mycobacterial"

Response: We have changed the text to mycobacterial.

4th page, 4th paragraph: change encephalitides to encephalitis.

Table 1: % lymphocytes on day 9 has not been added. Specify "Monkeypox virus PCR (Ct value)" instead of Monkeypox (Ct value)

Response: Thank you. The day 9 CSF was not further differentiated as the policy in our local lab is to provide full differential cell counts on those CSFs with a white cell count above 20

Editorial comments:

1. Please provide: one preferred degree qualification per author and indicate any full professors; affiliation details (department, institute, city, state, country) for each author; full institutional correspondence address for corresponding author.

2. Please check that all author details and affiliations are correct in both the main text and appendix investigator lists (if applicable). We do not guarantee that we will fix errors or omissions after publication (if your article is accepted)

3. Please add a conflict of interest statement that matches the ICMJE forms. Authors should be referred to by their initials in this section. If there are none, then please state “The authors declared no conflicts of interest” or “The other authors declared no conflicts of interest”.
4. Please add a contributors section, detailing specifically what each author did in the preparation of this manuscript. These statements should match those in your author statement forms.
5. We require written consent from any individuals who are cited in acknowledgments or personal communications. The following format can be used:
   “I permit <corresponding author> et al to list my name in the acknowledgments section of their manuscript and I have seen a copy of the paper <full article title>”
   “I permit <corresponding author> et al to cite a personal communication from me in their manuscript <full article title>”

We have added the consent from Marian Killip to be named in the acknowledgements.

6. We require confirmation that the paper has not been submitted to another journal, and has not been published in whole or in part elsewhere previously.

Response: This manuscript is not under consideration in any other journal and has not been published elsewhere.

7. For papers listed in references that are "in press" we need to see a galley proof and letter from the publisher stating that it is 'in press' as well as the full expected citation (ie, publication date/volume/issue etc).

NA

8. Images that have been published previously should be accompanied by a statement indicating permission to reproduce the image. If required, further assistance can be obtained from the editorial team. If you have borrowed published images from colleagues, you must obtain permission from the publisher of the paper, not just from the authors. If all the figures are your own and have not been published before then this requirement does not apply.

NA

9. Please ensure that you provide your figures in editable formats. For trial profiles (clinical trials) and study selection diagrams (systematic reviews and meta-analyses), figures must be provided as Word files (.doc or .docx) or powerpoint files (.ppt or .pptx) and made of boxes with editable text.
   For any statistical images such as histograms, survival or time-to-event curves, line graphs, scatter graphs, and forest plots you should provide editable vector files (ie, the original artwork generated by the statistical package used to make the image, typically by using "Export" or "Print to file" commands); our preferred formats for these files are .eps, .pdf, or .ai. Photographic images must be provided at a minimum of 300 dpi at 107 mm wide. We cannot guarantee accurate reproduction of images without these files. For more information, please see our artwork guidelines here.

10. References should be in the Vancouver style and numbered in the order in which they first appear in the manuscript. If the references "move" from the body text into tables or figures, please maintain the sequence of citation. Please ensure tables and figures are cited correctly in the body text to prevent the need for renumbering of references should the table and figure citations subsequently move. Please ensure that reference numbering throughout the manuscript is not inserted with electronic referencing software, such as Endnote.

11. Please supply a 150-200 word summary of your manuscript. References should not be cited in the Summary.

We have included a 111 word summary of our case.

12. Please supply a section entitled "Search strategy and selection criteria". This should state clearly the sources (databases, journals, or book reference lists, etc) of the material covered and the criteria used to include or exclude studies. Please state which search terms, languages and date ranges were used.

Response: We have added our search strategy to the text.

Data for this Grand Round were identified by searches of PUBMED and references from relevant articles and textbooks. Search terms were “monkeypox”, “encephalitis”, “transverse myelitis” “monkeypox, encephalitis”, “monkeypox, transverse myelitis”, “orthopoxvirus” and “orthopoxvirus, encephalitis”. Only English language papers were reviewed. No date restrictions were set in these searches.

13. If your paper is a systematic review, please check our Systematic reviews and meta-analyses formatting guidelines here to ensure that your paper is formatted correctly. Please note that you will need to provide a PRISMA flowchart if so.

NA

14. *The Lancet Infectious Diseases* endorses the SAGER guidelines for reporting of sex and gender information in study design, data analyses, results and interpretation of findings: https://www.equator-network.org/reporting-guidelines/sager-guidelines/. For all study types, we encourage correct use of the terms sex (when reporting biological factors) and gender (when reporting identity, psychosocial, or cultural factors). Where possible, please report the sex and/or gender of study participants, and describe the methods used to determine sex and gender. Separate reporting of data by demographic variables, such as age and sex, facilitates pooling of data for subgroups across studies and should be routine, unless inappropriate. Please also discuss the influence or association of variables, such as sex and/or gender, on your findings, where appropriate, and the limitations of the data.

NA

15. Please supply tables as separate Word files (not excel or fdf/pdf). Each row of data should be in a separate line. Please ensure that rows and columns are not tabbed; data should be entered in cell form.
16. Please supply the web appendix as a single PDF file, with the pages paginated - when you refer to an item in the appendix, please refer to the page number on which it appears, not the table or section. Please note that we will be unable to correct any errors in the web appendix, including errors or omissions in author names or affiliations, following publication; as such, please check carefully when submitting.
17. Please ensure ICMJE and author statement forms have been submitted for all authors.

We have uploaded these forms.

18. You need to make it clear that it's unknown whether pathogenesis is directly viral or immune-mediated (you treated both, so you are already aware of this).

Response: We have amended the text in line with the reviewers comments to clarify that we treated encephalitis likely secondary to mpx virus and post-infectious transverse myelitis treated with methylprednisolone / plasma exchange

19. You also must discuss the CSF PCR result in more detail (CT of 36 seems borderline).

Response: Many thanks for your comment regarding this and we agree it is an important one. We have responded to individual reviewers comments on this and have added the details regarding monkeypox specific testing.

20. Did you do a MPXV PCR in addition to the orthopox one?

Response: Monkeypox specific PCR were performed on the initial diagnostic samples, as shown in Table 1. The monitoring of confirmed cases of MPX at the stage of the UK epidemic was performed at the UKHSA Colindale reference lab using an Orthopox PCR. So MPXV PCR was only done CSF, but not on urine / other follow up sample types.