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| **TITLE OF CASE** |
| ***Herpes simplex virus encephalitis in a patient receiving ustekinumab associated with extensive cerebral oedema and brain-shift successfully treated by immunosuppression with dexamethasone***  *Van Den Tooren H1 , Bharambe V1, Silver N1, Michael BD1,2,3*  *1. The Walton Centre NHS Foundation Trust, Liverpool, UK*  *2. Department of Clinical Infection Microbiology and Immunology, Institute of Infection and Global Health, University of Liverpool, UK*  *3. NIHR Health Protection Research Unit for Emerging and Zoonotic Infection, University of Liverpool, UK* |
| **SUMMARY** |
| Herpes simplex virus encephalitis affects 2-4 people per million/yr. Patients who are immunocompromised can have atypical presentations of HSV encephalitis, including a lack of cerebrospinal fluid pleocytosis. We present a patient who was recieving ustekinumab therapy for psoriasis, which inhibits IL-12 and IL-23 signaling pathways. Initial presention was of a clinical syndrome suggestive of encephalitis, but the CSF sample did not show pleocytosis and he was discharged prior to the reporting of HSV PCR positivity. On representation he had worsening symptoms and imaging showed midline shift, indicating cerebral oedema despite the immune supressant effects of ustekinumab. He required intensive care unit support and treatment with high dose acyclovir and dexamethasone; after a month of treatment he made a good recovery. This case is the first to report a link between ustekinumab and HSV encephalitis, and also emphasises that imunocompromised patients can both a lack CSF pleocytosis and can also develop significant cerebral oedema which responds to immune suppression. |
| **BACKGROUND** |
| Hepes simplex virus (HSV) encephalitis is a condition of brain inflammation which has an estimated incidence of 2-4 cases per million per year worldwide (1). It is known that 10-15% of patients with encephalitis can have normal cerebrospinal fluid (CSF) at presentation, a proportion that increases in immunocompromise (2). Immunomodulatory therapies have expanded significantly in recent times, particularly for autoimmune conditions affecting the vascular, dermatological, and neurological systems. A recent development in the treatment for psoriasis includes ustekinumab, which inhibits the cytokines interleukin (IL) IL-12 and IL-23 binding to their cognate receptors (3). In this paper, we report the first case of HSV encephalitis in a patient receiving ustekinumab to the authors’ knowledge. This case also demonstrates that, as opposed to broad-spectrum immune-suppressive agents, these new more targeted immunomodulatory therapies can be associated with marked cerebral oedema and brain-shift, which was successfully treated by immunosuppression with dexamethasone. |
| **CASE PRESENTATION** |
| This 39 year old man presented to Accident and Emergency with a two day history of severe holocephalic headaches, neck stiffness and fever on a background of headaches and irritability for the last month. His past medical history included psoriasis, for which his only recent therapy was ustekinumab, an anti-IL-12/anti-IL-23 therapy, which he had been receiving for 1 year prior to presentation. Some years earlier he had been treated with methotrexate. Although initially treated with intravenous (iv) aciclovir, he was discharged following a lumbar puncture (LP) from which the only CSF abnormality on initial testing was a raised protein; the virological polymerase chain reaction (PCR) results were still pending at this time. An unenhanced computed tomography (CT) brain scan at this time was reported as normal. He represented one week later with on-going headaches, vomiting and had a reduced level of consciousness. A second LP was performed and he was re-started on iv aciclovir along with broad spectrum antibiotics for a suspected central nervous system (CNS) infection. Over the following two days he became more confused, his level of consciousness continued to decline, and he eventually required intubation. |
| **INVESTIGATIONS** |
| During the initial presentation the CSF showed 1 white cell per mm3, 0.65g/L protein and 4.1mmol/L glucose. Following the patient’s discharge PCR for HSV was reported to be positive, and pneumococcus, meningococcus and cryptococcus PCR was negative.  CSF analysis on the second presentation to hospital one week after discharge showed 556 white cells per mm3 (95% lymphocytes), 1.99g/L protein, glucose ratio 52%, and PCR for HSV remained positive. The imaging during the second presentation is shown in Figure. 1. The CT brain scan (1a and 1b) showed an area of low density in the right medial temporal lobe and evidence of midline shift. These abnormalities were further elucidated on magnetic resonance imaging (MRI), with medial temporal lobe T2-weighted hyperintensity, midline shift and uncal herniation (1c and 1d).  There was initial deterioration with a drop in consciousness level, and following transfer to the tertiary neurology centre, he underwent further MRI ( Figure. 2) which showed more pronounced oedema within the right temporal lobe associated with significant mid-line shift and uncal herniation. |
| **DIFFERENTIAL DIAGNOSIS** |
| The initial differential diagnosis at the first presenting hospital had been considered that of a non-CNS viral infection, as the LP had shown no evidence of CSF pleocytosis. On representation to the second hospital, both viral and bacterial CNS infections were considered and antibiotics stopped only after PCR evidence of HSV type-1 infection was demonstrated. |

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| **TREATMENT** |
| During the second admission to hospital, iv aciclovir, ceftriaxone and amoxicillin were given to cover a broad spectrum of CNS infections pending microbiology and virology investigation, albeit that viral encephalitis was considered the likely diagnosis. When the patient developed a reducing level of consciousness and imaging confirmed significant midline shift a Neurosurgical review for consideration of a decompressive craniectomy was under-taken and it was concluded that there was insufficient evidence to perform the procedure. Therefore, iv dexamethasone was commenced at 8mg/kg three times/day. Upon review by a Neurologist at the tertiary neurology centre the dexamethasone was increased to 10mg three times/day and, given the history of immune suppression, the dose of iv acyclovir was increased to 15mg/kg with on-going monitoring of renal function.  Following three weeks of iv aciclovir, a further LP was performed to see if HSV could still be detected by PCR. There were 370 white cells per mm3 (100% lymphocytes), protein was 0.34 g/L and glucose ratio was 78%; HSV PCR remained weakly positive and iv aciclovir was continued for a further seven days. The fourth LP*,* after 33 days of acyclovir, was performed and HSV could not be detected by PCR, therefore the iv aciclovir was stopped. Steroids were weaned gradually to discontinuation.  In parallel with the neurological management, this patient was supported in the intensive care unit (ICU) for over two weeks. He required ICU supportive care including intubation and ventilation primarily to prevent worsening of intracranial hypertension in the context of an agitated and low conscious level state. The patient received ventilator support for over three weeks necessitating a tracheostomy, and during this time he was also treated for a lower respiratory tract infection. |

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| **OUTCOME AND FOLLOW-UP** |
| With neurological improvement, the patient received rehabilitation support.Currently, two months after initial presentation, the patient remains well. He has had no seizures, receptive or expressive dysphasia, or clinical evidence of a relapse or autoimmune ‘pseudo-relapse’. He will receive community-based neuropsychological rehabilitation. |

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| **DISCUSSION** |
| HSV infects humans through mucous membranes, once the virus has entered the sensory nerves it travels to the ganglia where it enters the latent phase. The mechanisms by which HSV enters the CNS and causes encephalitis are incompletely understood. However the innate immune system and CD4+ and CD8+ T cells have all been shown to be involved (4). Ustekinumab prevents IL-12 and IL-23 interacting with their cognate receptors, which thus disrupts the production of IFN-γ that is induced by IL-12, IL-17, and IL-22 which are in turn induced by IL-23. IL-12 and IL-23 signalling pathways are initiated by cells of the innate immune system, such as dendritic cells and tissue-resident macrophages, and effect TH cell differentiation (5). This is the first reported case of HSV encephalitis in a patient taking ustekinumab, and could suggest that IL-12 and IL-23 signalling pathways are involved in the immunological response to HSV in the CNS.  The first CSF sample in this patient was not suspected to indicate CSF infection because the white cell count was not raised, glucose ratio was normal and there was only mildy increased protein. However, immunocompromise of various causes have been shown to lead to atypical presentations of HSV encephalitis, particularly sub-acute presentations and the lack of CSF pleocytosis (6–8). Despite the lack of pleocytosis in the CSF, the patients initial HSV PCR was positive in keeping with the pattern of HSV encephalitis in immunocompromised individuals (8). This case reitterates the importance of both suspecting encephalitis in patients who are on immunomodulatory therapies and also awaiting negative PCR result prior to discontinuation of antiviral therapy. National UK guidelines recommend that HSV encephalitis can be excluded if two separate LPs, separated by 48hrs, fail to identify HSV by PCR and an MRI brain scan is normal, if performed after at least 72hrs of symptoms (2).  These same guidelines suggest performing an urgent LP on presentation, unless there are clear clinical contraindications, and iv acyclovir at 10mg/kg started within 6 hours of admission (2). On the second presentation these guidelines were followed. However, the dose of acyclovir was increased to 15mg/kg due to the history of immunocompromise and high dose dexamethasone used under specialist supervision. The use of corticosteroids in encephalitis is controversial, but a randomised control trial is currently being performed to evaluate its place in the management of HSV encephalitis (2). This patient was not eligible for the trial as dexamethasone had already been commenced prior to consideration for randomisation due to the declining conscious level secondary to extensive cerebral oedema and midline shift. In this case decompressive hemicraniectomy was considered but not performed, as the risks potentially outweighed the benefits in the absence of any evidence to support this operation. There have been a small number of anecdotal case reports of successful recovery following decompressive hemicraniectomy in HSV encephalitis but evidence for large cohorts or controlled trials is lacking (9).  Whilst the patient had an excellent outcome following the treatment outlined we cannot exclude the possibility that he may have had a similar outcome had iv dexamethasone not been prescribed. Nevertheless, the progressive decline in consciousness was associated with significant cerebral oedema, midline shift, and uncal herniation despite acyclovir; these features of raised intracranial pressure are typically associated with a poor prognosis, suggesting that broad immunosuppression with dexamethasone may have contributed to his positive outcome (10) . Indeed, in observational studies of adjunctive dexamethasone improved outcomes have been reported and in a murine model of HSV encephalitis dexamethasone was associated with markedly reduced cerebral oedema in response to this treatment (11,12) . Whilst IL-12 and IL-23 have important roles in TH1 and TH17 differentiation respectively as well as natural killer responses, the more broad effects of dexamethasone may reduce cerebral oedema through multiple mechanisms including stabilisation of blood-brain barrier permeability and reduced neutrophil transmigration, as has been demonstrated in an *in vitro* model of viral encephalitis (13). |

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| **LEARNING POINTS/TAKE HOME MESSAGES** |
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* Immunocompromised patients with encephalitis can have relatively normal CSF appearances. When encephalitis is suspected, viral PCR for herpes viruses is mandatory, even where there is no CSF pleocytosis, and required to be proven negative before withdrawing antiviral acyclovir treatment. National UK guidelines recommend that two LPs should be negative for HSV and an MRI normal before HSV is excluded in a patient with suspected encephalitis.
* There are increasing immunomodulatory therapies for ever increasing ranges of medical conditions and the presence of opportunistic infection must be considered when patients on therapies such as ustekinumab present with clinical features suggestive of a possible CNS infections.
* Decompressive hemicraniectomy has been described in HSV encephalitis, but there is no strong evidence to support its use. It is not possible in individual anecdotal cases to determine if such treatment approach is worthwhile and higher-level evidence for the management of intracranial pressure in encephalitis is required.
* Despite the immunosuppressive effects of ustekinumab this patient developed marked cerebral oedema with midline shift and uncal herniation, which was successfully treated by broad immunosuppression with dexamethasone.

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| **REFERENCES** 1. Bradshaw MJ, Venkatesan A. Herpes Simplex Virus-1 Encephalitis in Adults: Pathophysiology, Diagnosis, and Management. Neurotherapeutics [Internet]. 2016 [cited 2018 Dec 15];13:493–508. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4965403/pdf/13311\_2016\_Article\_433.pdf  2. Solomon T, Michael BD, Smith PE, Sanderson F, Davies NWS, Hart IJ, et al. Management of suspected viral encephalitis in adults--Association of British Neurologists and British Infection Association National Guidelines. J Infect [Internet]. Elsevier; 2012 Apr 1 [cited 2018 Dec 15];64(4):347–73. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22120595  3. Schadler ED, Ortel B, Mehlis SL. Biologics for the primary care physician: Review and treatment of psoriasis. Disease-a-Month [Internet]. 2018 Jul [cited 2018 Dec 15]; Available from: https://linkinghub.elsevier.com/retrieve/pii/S0011502918300956  4. Zhang J, Liu H, Wei B. Immune response of T cells during herpes simplex virus type 1 (HSV-1) infection. J Zhejiang Univ Sci B [Internet]. Zhejiang University Press; 2017 [cited 2018 Dec 15];18(4):277–88. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28378566  5. Teng MWL, Bowman EP, McElwee JJ, Smyth MJ, Casanova J-L, Cooper AM, et al. IL-12 and IL-23 cytokines: from discovery to targeted therapies for immune-mediated inflammatory diseases. Nat Med [Internet]. Nature Publishing Group; 2015 Jul 29 [cited 2018 Dec 15];21(7):719–29. Available from: http://www.nature.com/articles/nm.3895  6. Wu M, Huang F, Jiang X, Fan Z, Zhou H. Herpesvirus-Associated Central Nervous System Diseases after Allogeneic Hematopoietic Stem Cell Transplantation. PLoS One [Internet]. 2013 [cited 2018 Dec 16];8(10):77805. Available from: www.plosone.org  7. Jakob NJ, Lenhard T, Schnitzler P, Rohde S, Ringleb PA, Steiner T, et al. Herpes simplex virus encephalitis despite normal cell count in the cerebrospinal fluid. Crit Care Med. 2012;40(4):1304–8.  8. Meyding-Lamadé U, Strank C. Herpesvirus infections of the central nervous system in immunocompromised patients. Ther Adv Neurol Disord [Internet]. SAGE Publications; 2012 Sep [cited 2018 Dec 15];5(5):279–96. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22973424  9. Jouan Y, Grammatico-Guillon L, Espitalier F, Cazals X, François P, Guillon A. Long-term outcome of severe herpes simplex encephalitis: a population-based observational study. Crit care [Internet]. 2015 [cited 2018 Mar 22];19:345. Available from: https://ccforum.biomedcentral.com/track/pdf/10.1186/s13054-015-1046-y?site=ccforum.biomedcentral.com  10. Sili U, Kaya A, Mert A. Herpes simplex virus encephalitis: Clinical manifestations, diagnosis and outcome in 106 adult patients. J Clin Virol [Internet]. Elsevier; 2014 Jun 1 [cited 2019 Jan 3];60(2):112–8. Available from: https://www.sciencedirect.com/science/article/pii/S1386653214001024?via%3Dihub  11. Kamei S, Sekizawa T, Shiota H, Mizutani T, Itoyama Y, Takasu T, et al. Evaluation of combination therapy using aciclovir and corticosteroid in adult patients with herpes simplex virus encephalitis. J Neurol Neurosurg Psychiatry [Internet]. 2005 [cited 2019 Jan 3];76:1544–9. Available from: www.jnnp.com  12. Meyding-Lamadé UK, Oberlinner C, Rau PR, Seyfer S, Heiland S, Sellner J, et al. Experimental Herpes Simplex Virus Encephalitis: A Combination Therapy of Acyclovir and Glucocorticoids Reduces Long-Term Magnetic Resonance Imaging Abnormalities. J Neurovirol [Internet]. Springer-Verlag; 2003 Jan [cited 2019 Jan 3];9(1):118–25. Available from: http://link.springer.com/10.1080/13550280390173373  13. Patabendige A, Michael BD, Craig AG, Solomon T. Brain microvascular endothelial-astrocyte cell responses following Japanese encephalitis virus infection in an in vitro human blood-brain barrier model. Mol Cell Neurosci [Internet]. 2018 Jun [cited 2019 Jan 3];89:60–70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29635016 |
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| **FIGURE/VIDEO CAPTIONS** |
| Figure 1 Imaging on re-presentation to hospital.  A and B: CT Brain . C and D MRI brain (coronal FLAIR and Axial T2-weigted sequences).  Figure 2 Imaging taken following deterioration at the tertiary neurology centre  The left MR image is a coronal slice of T2 FLAIR sequence , and right shows an axial slice of T2 sequence. Both images show worsening of the marked right medial temporal lobe T2 hyperintensity and worsening midline shift compared to Figure.1 |

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| **PATIENT’S PERSPECTIVE** |

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