A Case Report of Herpes Simplex Virus Encephalitis during Natalizumab Treatment for Relapsing Remitting Multiple Sclerosis

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Background

- Natalizumab is indicated as monotherapy for the treatment of patients with relapsing remitting multiple sclerosis (MS).
- Natalizumab inhibits migration of lymphocytes into the central nervous system (CNS), which potentially impairs immune surveillance for CNS infections.
- Natalizumab-associated reactivation of John Cunningham (JC) virus, causing progressive multifocal leukoencephalopathy (PML), is well documented.
- Natalizumab treatment for MS is less clearly linked to increased risk of other viral infections.
- Recent case series by Fine et al[1] reported 20 natalizumab-treated MS patients who developed CNS herpes simplex virus (HSV) infections.
- Potential role of prior immunosuppressant (IS) exposure in enhancing the risk of CNS HSV infection could not be determined.[1]

Objective

- To describe a non-fatal case of herpes simplex virus encephalitis (HSE) in a patient with fulminant MS treated with natalizumab without prior IS or disease modifying therapy (DMT) exposure.

Case Report

- 38 year-old man with fulminant MS [Figure 1] was treated with natalizumab as initial therapy with first infusion on June 07, 2013.
- On September 24, 2013, after 4 monthly treatments with natalizumab, patient was found unresponsive following a seizure.
- MRI Brain showed a new T2/FLAIR hyperintense lesion in the left temporal lobe with associated focal edema and restricted diffusion [Figure 2].
- HSV type 1 DNA was detected in cerebrospinal fluid (CSF) by PCR; CSF JC virus PCR was negative.
- Overall, patient responded well to 6 weeks of IV acyclovir therapy that was started on day of HSE onset, followed by 4 out of 6 planned months of oral valacyclovir thus far.
- Subsequent MRI Brain 2 weeks after ictus showed interval development of petechial blood products in the left temporal lobe and insular region [Figure 3].

Results

April 29, 2013

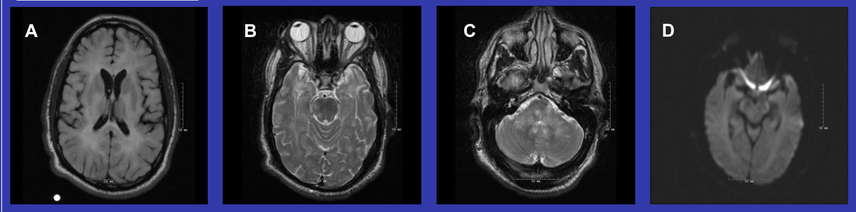

Figure 1: Baseline MRI Brain before initiation of natalizumab. Extensive T2/FLAIR lesion burden throughout the bilateral cerebral hemispheres and posterior fossa, characteristic of MS (A-C). No evidence of restricted diffusion on DWI sequences (D).

September 24, 2013

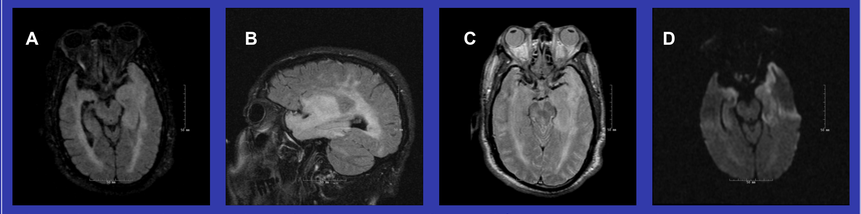

Figure 2: MRI Brain at the time of HSE onset. Confluent T2/FLAIR hyperintensity throughout the left temporal lobe with diffuse edema and enlargement of the left amygdala and hippocampal formation (A-C). New restricted diffusion on DWI in the left temporal lobe (D).

October 08, 2013

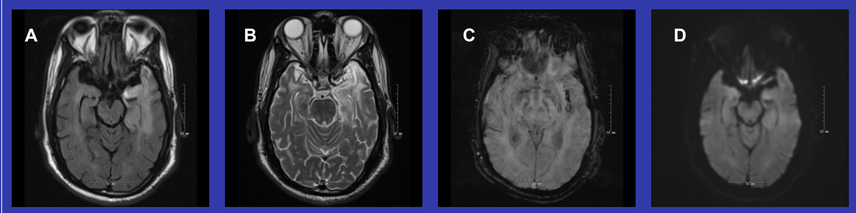

Figure 3: MRI Brain during HSE, after 2 weeks of IV acyclovir. Interval development of more confluent T2/FLAIR hyperintensity (A-B) with associated petechial blood products in the left medial temporal lobe and insula on SWI images (C). Interval resolution of restricted diffusion on DWI sequences (D).

March 24, 2014

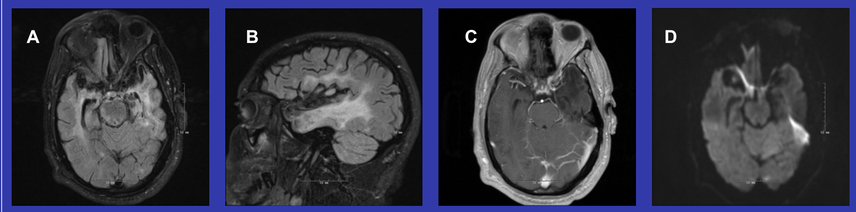

Figure 4: MRI Brain after acute HSE. Interval development of encephalomalacia in the left anterior temporal lobe, as illustrated on axial and sagittal FLAIR (A-B) and T1-weighted sequences (C). No restricted diffusion on DWI sequences (D).

Case Report (cont.)

- Repeat CSF studies after completion of 6 weeks of IV antiviral therapy showed no detectable HSV DNA.
- Patient has demonstrated residual neuropsychiatric disturbances since ictal event with otherwise near normal neurological examination.
- Neuropsychiatric symptoms included severe anterograde amnesia and impaired executive functioning.
- Repeat MRI Brain 6 months after HSE onset showed extensive encephalomalacia in the left temporal lobe [Figure 4] with otherwise radiographically stable MS lesion load.
- Re-starting DMT was favored in light of previous fulminant disease and risk of reactivation since stopping natalizumab.
- Patient and his family remain hesitant to re-start therapy, and he is currently being closely monitored off of DMT.

Conclusions

- Our case and previously reported cases[1-2] suggest there is increased risk of CNS HSV infection with natalizumab therapy, even without prior IS exposure.
- Natalizumab label was recently changed to include a black box warning about CNS herpes infections.[3]
- Reported cases demonstrated good response with early detection and appropriate treatment with antiviral agents.
- Prolonged neuropsychiatric changes have been described in a previous case of HSE during natalizumab treatment for MS.[2]
- In addition to monitoring for PML, providers caring for MS patients treated with natalizumab should remain vigilant for other CNS infections.

References

1. Fine AJ, Sorbello A, Kortepeter C, et al. Central nervous system herpes simplex and varicella zoster virus infections in natalizumab-treated patients. *Clin Infect Dis.* 2013;57(6):849-852.
2. Kwiatkowski A, Gallois J, Bilbault N, et al. Herpes encephalitis during natalizumab treatment in multiple sclerosis. *Mult Scler*. 2012;18(6):909-911.
3. Highlights of Prescribing Information for Tysabri (natalizumab) injection. Available at: http://www.tysabri.com/pdfs/I61061-13_PI.pdf. Accessed December 2013.

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