Natalizumab and rapidly evolving central nervous system lymphoma in VigiBase

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Background

Natalizumab, an α4b1-integrin inhibitor, limits lymphocyte passage through the blood-brain barrier. It is approved for the treatment of relapsing-remitting multiple sclerosis (RRMS) via monthly infusions. Central nervous system lymphoma (CNSL) is rare, with incidence increasing with age, particularly after age 55[1]. Risk factors include immunosuppression and EBV infection. MS and CNSL may overlap and biopsy is preferred for diagnosis, with imaging being less reliable[2]. A two-year natalizumab study showed no impact on incidence of malignancies[3].

Aim

To assess the drug-adverse event combination (DEC) natalizumab with MedDRA Preferred Term "Central nervous system lymphoma" in VigiBase, alongside published literature cases.

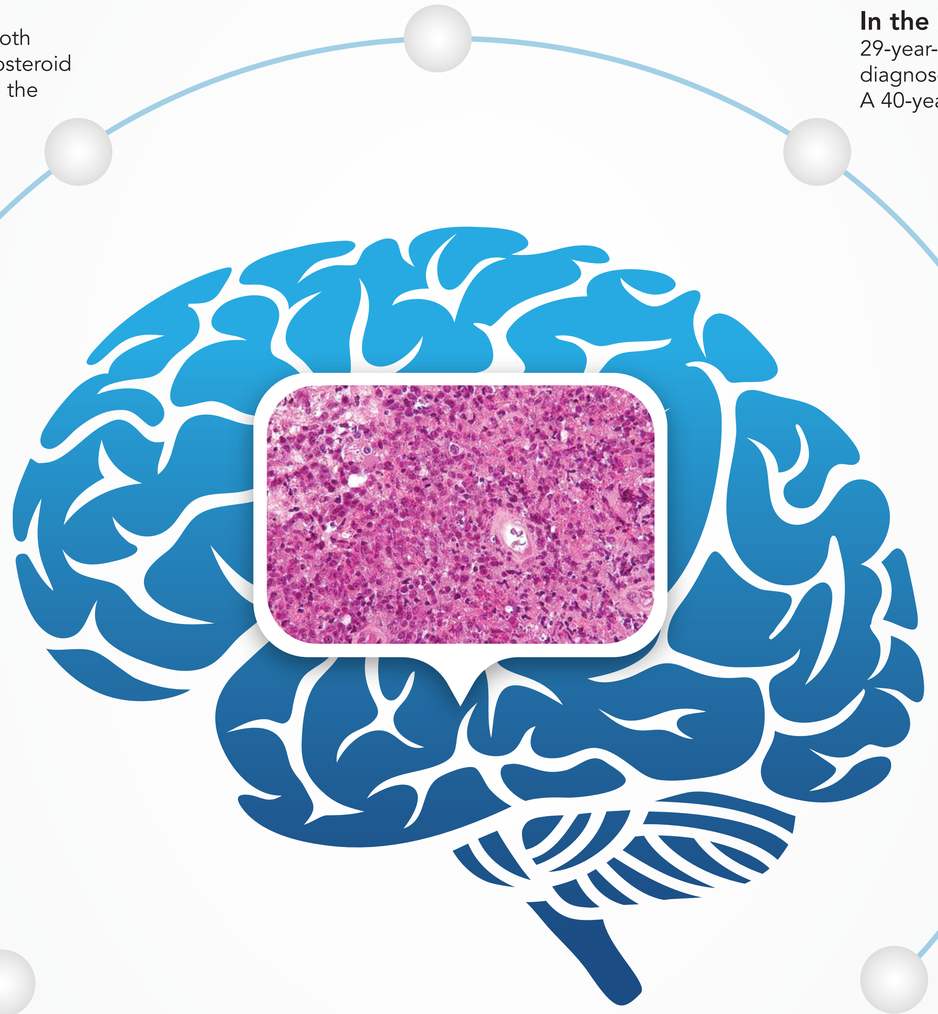
Methods

Reports of the DEC until May 2015 were extracted from VigiBase. Literature cases were matched and duplicates removed. Clinical findings, co-reported terms and drugs, and duration of treatment were appraised.

Chronic immunosuppressive treatment can predispose patients to CNSL. Immunosuppressants such as azathioprine are labelled for this condition. No statistical association was found between multiple sclerosis and CNSL.

CNSL may be misdiagnosed as MS, via imaging, making biopsy more reliable. Both conditions respond positively to high corticosteroid doses. However, corticosteroids may reduce the power of biopsy to tell MS from CNSL.

In the literature there were 5 cases in total. A 29-year-old, HIV- and EBV-negative male was diagnosed with CNSL after 21 courses of natalizumab. A 40-year-old, EBV-negative male, only after two.



Central nervous system lymphoma (CNSL) is a rare cancer, most commonly of the diffuse large B-cell type, that mostly affects males. Risk factors include: Epstein-Barr virus (EBV), profound immunosuppression (i.e. HIV-AIDS), age > 65.

VigiBase patients were relatively young, between 28 and 59 years of age, with a median of 44. Natalizumab was administered in 1-21 cycles, with 3 in median. Only two cases reported concomitant immunosuppressants, but it is likely patients received some before natalizumab. Two patients were misdiagnosed with MS.

Natalizumab has been approved for use in severe relapsing remitting multiple sclerosis (RRMS), for patients that do not respond to adequate treatment, with one or more gadolinium enhancing lesions or whose lesions have worsened significantly in between two MRIs.

Rapidly growing CNSL lesions were reported in a patient, after only 2 natalizumab courses. This is consistent with the literature. A proposed mechanism involves reduced central nervous system immunosurveillance promoted by natalizumab.

Multiple sclerosis is a myelin-disrupting autoimmune disease, accompanied by loosening of the blood-brain barrier. Multiple sclerosis may lead to vision loss, fatigue and gait disturbances. It is managed with immunosuppressants: in acute manifestations with methylprednisolone, while chronically with interferon, azathioprine, fingolimod, or other monoclonal antibodies.

The VigiBase case series was similar to literature cases, with respect to time to diagnosis, patients' immunocompetence and relatively young age, with lesions described as rapidly evolving. Therefore, it could be worth reviewing and updating the available safety information on natalizumab.

Results

There were 12 cases whereof 5 from literature with an IC of 3.12 indicating the DEC was occurring more often than expected. There were eight females and four males; age range: 28-59 years (median 44). Natalizumab was the only suspect in 11, co-suspect in one with other immunosuppressants. Duration of treatment ranged from 1 to 21 cycles (median 3). Six cases were confirmed by biopsy, 3 patients were EBV/HIV negative, with the rest having unknown EBV/HIV status. Two were first misdiagnosed with MS but after 3 courses the diagnosis was changed to CNSL. In another case of a 41-year-old female, the perceived "MS" lesions grew rapidly after 2 courses raising suspicion of the later diagnosed CNSL.

Two literature cases of patients were outside the expected CNSL age range; a 40-year-old male diagnosed with RRMS via MRI, CSF analysis and biopsy. Azathioprine treatment failure was followed by natalizumab with a CNSL diagnosis after 21 courses. EBV and HIV tests were negative[4]. A second EBV negative 40-year-old male was diagnosed with CNSL after two courses of natalizumab; authors postulate that natalizumab may promote the progression of pre-existing lesions[5].

Conclusion

Several VigiBase case reports present similarities with the well described literature cases, being EBV/HIV negative and presenting with rapid lymphoma progression. Reduced lymphocyte CNS surveillance, mediated by natalizumab mechanism of action, may accelerate pre-existing CNSL growth. Despite uncertainties regarding a causal role of natalizumab[6], we believe VigiBase data adds sufficient evidence to discuss an update to the natalizumab safety profile.

Footnote: as of 04-2017 an additional 13 cases, still under assessment by UMC, have been reported to VigiBase.

References
1. Ostrom QT, Gittleman H, Liao P, Rouse C, Chen Y, Dowling J, et al. CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2007–2011. Neuro-Oncology. 2014;16(Suppl 4):iv1-iv63.
2. Hunt MA, Jahnke K, Murillo TP, Neuwelt EA. Distinguishing primary central nervous system lymphoma from other central nervous system diseases: a neurosurgical perspective on diagnostic dilemmas and approaches. Neurosurgical focus. 2006;21(5):E3.
3. Polman CH, O'Connor PW, Havrdova E, Hutchinson M, Kappos L, Miller DH, et al. A Randomized, Placebo-Controlled Trial of Natalizumab for Relapsing Multiple Sclerosis. New England Journal of Medicine. 2006;354(9):899-910.
4. Schweikert A, Kremer M, Ringel F, Liebig T, Duyster J, Stüve O, et al. Primary central nervous system lymphoma in a patient treated with natalizumab. Annals of neurology. 2009;66(3):403-6.
5. Phan-Ba R, Bisig B, Deprez M, De Prijck B, Delrue G, Herens C, et al. Primary central nervous system lymphoma in a patient treated with Natalizumab. Annals of Neurology. 2011;69(6):1060-1.
6. Bozic C, LaGuette J, Panzara MA, Sandrock AW. Natalizumab and central nervous system lymphoma: No clear association. Annals of Neurology. 2009;66(3):261-2.

Disclosure
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