UNUSUAL DETERIORATION IN A PATIENT WITH MULTIPLE SCLEROSIS ON NATALIZUMAB THERAPY

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Natalizumab is an effective treatment in patients with highly active relapsing-remitting multiple sclerosis (RRMS). However, its positive therapeutic effects have to be weighed against the potential serious adverse event of progressive multifocal leukoencephalopathy (PML). Thus, whenever patients with MS on natalizumab develop uncommon and progressive neurologic symptoms, the suspicion of PML has to be raised. The risk of PML becomes higher with increasing duration of natalizumab treatment, prior immunosuppressive treatment, and JC virus (JCV) antibody seropositivity.1 We here report a case of MS in which unusual symptoms in the context of 5 years of natalizumab treatment and seroconversion to JCV antibody positivity led to the initial suspicion of PML and a final diagnosis of Creutzfeldt-Jakob disease (CJD).

Case report. A 42-year-old woman with RRMS was admitted because of rapidly progressive symptoms including neuropsychological deficits and severe trunk ataxia. She had received her diagnosis of MS 15 years ago. At that time, treatment with interferon-β-1b 250 μg SC every other day was initiated but had to be ceased 5 months later due to severe icterus and toxic liver necrosis. Subsequently, treatment was changed to daily SC injections of glatiramer acetate 20 mg. Ten years later, she was escalated to natalizumab because of ongoing and increasing disease activity. In March 2013, after almost 5 years of monthly infusions with natalizumab, she complained of tiredness, difficulties in walking, and problems with memory and concentration. The patient was admitted to a neurorehabilitation clinic in May under the assumption of a conversion to secondary chronic progressive MS. Subsequent brain MRIs in May and June depicted neither active/new MS lesions nor other abnormalities. Nonetheless, natalizumab was stopped after a total of 60 infusions due to suspicion of PML. Serologic blood testing for the first time showed antibodies against JCV, while PCR was negative for JCV in both blood and CSF. This was when the patient was admitted to our department, where she presented with psychomotor slowing, severe cognitive impairment in multiple domains, cerebellar dysarthria, positive primitive reflexes, and pronounced trunk ataxia. A new brain MRI demonstrated T2 hyperintense bilateral symmetric signal abnormalities in the striatum with accompanying diffusion restriction (figure), characteristic of sporadic CJD (sCJD). Lumbar puncture yielded excessively high CSF tau protein levels (8,199 pg/mL) and positivity for the 14-3-3 protein.

Subsequent EEGs revealed nonepileptic diffuse generalized abnormalities without triphasic spikes. The patient had an unremarkable family history and had not undergone neurosurgical/ophthalmic interventions. She did not have unusual eating habits and had not traveled to foreign countries. Over the following weeks, she turned akinetically mutistic, showed intermittent myoclonic jerks, and finally became fully bedridden. Probable sCJD was diagnosed according to current criteria.2 The patient died 1 month after discharge to a nursing home. Brain autopsy confirmed sCJD and showed typical MS demyelination areas (figure); there was no evidence of PML (no antibody detection against JCV antigen).

Discussion. While the primary suspicion in patients with MS on natalizumab who develop unusual neurologic symptoms is certainly PML, we here present the case of such a patient in whom these symptoms were due to sCJD. This stresses the need to scrutinize alternative diagnoses in such a scenario. Although a definitive diagnosis of CJD needs autopsy confirmation, clinical, laboratory, and brain imaging features were highly suggestive of this disease in our patient and guided the patient evaluation in this direction.

In clinical practice, any relapse in patients with MS treated with natalizumab should raise suspicion of PML. In contrast to MS, symptoms in patients with PML occur more subacutely and are continuously progressive. In addition, atypical symptoms such as seizures, rapid cognitive dysfunction, hemianopia, or altered mental status suggest PML rather than active MS. The wide clinical spectrum of PML3 comes from the fact that nearly every part of the brain can be affected, which is not too dissimilar to the diffuse spongiform degeneration of CJD. However, the co-occurrence of the 4 cardinal clinical
features (dementia, visual/cerebellar signs, pyramidal and extrapyramidal symptoms, and akinetic mutism) and especially the observation of myoclonic jerks pointed to the diagnosis of CJD in our patient.2 Another important diagnostic clue that argued against PML and supported CJD diagnosis in this case was neuroimaging. MRI patterns that distinguish PML from MS lesions have recently been published.4 In our patient, no MRI evidence for progression of MS could be seen as there were no new T2/fluid-attenuated inversion recovery (FLAIR) lesions in comparison with previous available MRI scans, and there were especially no MRI changes suggestive of PML. Although basal ganglia structures are often involved in PML, this involvement usually occurs in a patchy and unilateral fashion, while symmetric bilateral and sharp-edged signal hyperintensity of the caudate nucleus and putamen on FLAIR and diffusion-weighted imaging sequences is very specific for CJD.2 Finally, CSF analysis was negative for JCV DNA using PCR with an ultrasensitive assay, 5 whereas it was positive for the 14-3-3 protein with an excessively increased tau protein level.

Given the low incidence rate of CJD of 0.1/100,000,6 it is tempting to speculate about whether the patient’s primary disease or the long-term treatment with natalizumab predisposed her to develop this particular condition. However, the absence of reports on the occurrence of sCJD in patients with MS, especially those on natalizumab, and no clear pathophysiologic links make a chance association most likely.

In summary, our case report demonstrates that increased vigilance and a diligent workup of differential diagnoses are demanded in patients with MS who develop unusual symptoms and signs under therapy with natalizumab and other immunomodulating and immunosuppressive treatments.

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Figure MRI and histopathologic features of CJD and MS

Fluid-attenuated inversion recovery (FLAIR) sequences on MRI show a symmetric hyperintensity in the caudate nucleus and putamen (A.a) and a diffusion restriction in these areas (diffusion-weighted imaging, A.b), suggestive of Creutzfeldt-Jakob disease (CJD). Histopathology (×40 magnification) in A.c demonstrates positivity of pathologic plaques highlighted by reactivity of antibodies against the prion protein antigen (arrows; prion protein monoclonal antibody [clone 12F10], Bertin Pharma, Montigny-le-Bretonneux, France). Images B.a and B.b depict typical periventricular multiple sclerosis (MS) lesions on FLAIR MRI scans and corresponding demyelination in these areas (B.c, Klüver-Barrera staining, ×10 magnification).
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