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Article in *Revue Neurologique* · March 2017

DOI: 10.1016/j.neurol.2017.03.008

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Short communication

Multiple immune disorders after natalizumab discontinuation: After the CIRIS, the SIRIS?

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INFO ARTICLE

Article history:

Received 5 March 2016
Received in revised form
4 October 2016
Accepted 9 March 2017
Available online xxx

Keywords:

Multiple sclerosis
Immunosuppressor
Natalizumab (Tysabri)
Withdrawal
Immune reconstitution
inflammatory syndrome (IRIS)

ABSTRACT

Natalizumab (NTZ) is an effective treatment for patients with highly active relapsing remitting multiple sclerosis (MS). However, when the therapy must be interrupted, it is important to anticipate the withdrawal to avoid reactivation or disease rebound. Described here is the case of a 35-year-old woman, with a past history of beta thalassemia, bulimia and asthma, who was diagnosed with MS at age 26. She was treated initially with first-line subcutaneous (sc) immunomodulatory treatments. However, due to liver toxicity, interferon beta-1a sc was interrupted and replaced by glatiramer acetate treatment, which was well tolerated and used for several years. Unfortunately, disease progression with numerous relapses and contrast enhancement on brain MRI led to initiation of NTZ treatment. After more than 2 years of treatment, NTZ was interrupted because of pregnancy, and the patient was again put on glatiramer acetate. Eight weeks after interruption of NTZ therapy, the first signs of diabetes were observed, together with an increase in blood levels of hepatic enzymes, skin reactions such as angioedema and giant urticaria, and hypothyroidism requiring hormone supplementation. The patient delivered her baby without complications, and NTZ was reintroduced several months later. At the present time, the patient's hypothyroidism, diabetes and increased blood levels of hepatic enzymes persist, although no new skin reactions have been observed. Withdrawal of NTZ can not only lead to reactivation of the disease or its rebound, but also to autoimmune manifestations within the framework of immune reconstitution inflammatory syndrome (IRIS). This risk needs to be considered when therapy has to be interrupted, especially when a personal and/or familial past history of autoimmune disease is present.

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1. Introduction

Natalizumab (NTZ) is a monoclonal antibody that provides effective treatment for patients with highly active relapsing

remitting multiple sclerosis (MS). However, a major therapeutic issue is related to the fact that NTZ is associated with an elevated risk of progressive multifocal leukoencephalopathy (PML), caused by local reactivation of John Cunningham (JC) virus [1], and the discontinuation of NTZ treatment must be

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<http://dx.doi.org/10.1016/j.neurol.2017.03.008>
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anticipated and followed closely. Disease reactivation or even its rebound has been reported within 6 months of stopping NTZ, especially in patients who presented with high disease activity the year before treatment initiation [2]. Adverse events, including disease rebound and immune reconstitution inflammatory syndrome (IRIS), after cessation of NTZ are well recognized and should not be underestimated. IRIS appears following recovery from local immunodeficiency, and leads to an uncontrolled inflammatory response to infectious agents and, subsequently, tissue damage. Initially, IRIS was described in human immunodeficiency virus (HIV)-positive patients after immune recovery following initiation of antiretroviral therapy [3]. However, rebound-mimicking IRIS has also been described in patients following withdrawal of NTZ.

2. Observation

A right-handed woman with a past history of beta thalassemia, bulimia, conduction block and asthma was diagnosed with MS in 2002 at age 26. Her mother and one of her sisters had type 2 diabetes (T2D) and hypothyroidism. First-line subcutaneous (sc) immunomodulatory treatments were initiated in 2002. However, interferon beta-1a sc was interrupted after 3 months of therapy due to liver toxicity, and was replaced by glatiramer acetate (GA), another first-line sc treatment, which she received for several years before it had to be withdrawn due to ineffectiveness and the appearance of local skin reactions. The patient then received no treatment for 6 months. However, disease progression with numerous relapses and contrast enhancement on magnetic resonance imaging (MRI) led to initiation of NTZ treatment, which was well tolerated and effective. Her Expanded Disability Status Scale (EDSS) score was 3, with deficiency of epicritic sensitivity and ataxia.

After several years of NTZ treatment and no relapses, therapy was discontinued in November 2011 because of an unscheduled pregnancy, with her last perfusion in October 2011. Therapy was switched again to GA in January 2012, which was well tolerated. However, at that time and 2 months into the pregnancy, the first signs of T2D were observed, and its treatment was started. Hepatic enzyme levels continued to increase, necessitating further study of liver function, including hepatic biological function, liver ultrasound, hepatic MRI and liver biopsy. The two major findings were hepatomegaly and non-alcoholic steatosis. Blood tests revealed no abnormalities except for seropositivity for hepatitis E virus (HEV), but this was not confirmed by polymerase chain reaction (PCR) analysis. In March 2012, 4 months after NTZ cessation, skin reactions such as angioedema and giant urticaria were observed and treated with high doses of antihistamine drugs (tryptase enzymes and anti-IgE antibodies were found negative). A few weeks later, the patient developed hypothyroidism, which required hormone supplementation.

These diverse clinical and biological immune manifestations led to interruption of the patient's GA treatment in March 2012 as well as her antidiabetes drug (metformin). The patient delivered her baby on 24 July 2012 and, postpartum, prophylactically received high-dose corticotherapy (over a period of 6 months). The choice of second-line treatment in

November 2012 was reduced to fingolimod vs NTZ. The latter was chosen, considering her past cardiac history, T2D and high risk of varicella-zoster virus (VZV) primary infection (seronegative). At present, the patient is still being treated for T2D and hypothyroidism. However, she has presented with no new dermatological symptoms, and her liver enzymes have returned to normal levels.

3. Discussion

In this case report, our patient presented with several immune manifestations in the weeks following NTZ discontinuation. She had multiple factors potentially predisposing to the development of cutaneous reactions, T2D, hypothyroidism and perturbation of liver enzymes. In fact, she had an increased susceptibility to developing T2D and hypothyroidism due to her family history, and the liver enzyme perturbations making her sensitive to treatment might have been a reflection of a predisposition to developing autoimmune reactions. As the patient was receiving GA treatment for several weeks before the appearance of the autoimmune reactions, the possible implication of that agent cannot be totally discounted, as the treatment is known to generate reactive polyclonal antibodies that can cross-react with myelin epitopes such as myelin basic protein (MBP). Anti-GA antibodies may also be implicated in allergenic reactions and autoimmune adverse events, such as anaphylactic shock, lymphadenopathy, livedo-like dermatitis, lymphocytic infiltration and erythema nodosum [4]. However, to our knowledge, no T2D or hypothyroidism related to GA treatment has been described.

Three hypotheses might explain the appearance of the patient's various immune manifestations following NTZ discontinuation. First of all, it is well acknowledged that any autoimmune disease is associated with a frequency of 30% of having another, additional autoimmune disease. The second hypothesis is that autoimmune manifestations may be induced by immunomodulatory treatments, as has been described with alemtuzumab (Graves' disease, thrombocytopenia, autoimmune hemolytic anemia, T2D) [5,6], rituximab (hypothyroidism, arthropathies) and NTZ (hemolytic anemia, liver disease, arthropathies). These autoimmune reactions are different from the type-1 IgE-mediated reactions described in the first 6 months of starting NTZ and with immunization against NTZ, with detection of antibodies against the drug. The third hypothesis is that these autoimmune manifestations could be viewed as a systemic immune reconstitution inflammatory syndrome (SIRIS) following NTZ withdrawal. It is well known that after stopping the drug, both disease and inflammatory rebound can arise. Therefore, it is possible that the administration of NTZ could limit peripheral blood vessel permeability and, in the case of our patient, could have damped down any peripheral inflammation. Thus, therapy withdrawal would then have induced a highly inflammatory state, and the rebound might be particularly aggressive if the withdrawal is due to pregnancy [7].

Factors linked to a high probability of the appearance of IRIS are well documented in HIV-positive patients following the initiation of antiretroviral therapy. IRIS has also been

described in patients with NTZ-induced PML. In the absence of virus, this rebound effect has been referred to as a central nervous system (CNS) immune reconstitution inflammatory syndrome (CIRIS). It has also been postulated that this may arise due to concerted waves of T and B cells re-entering the brain once the blood-brain barrier has become permeable to immune cells. In this case, neurologists would have to deal with disease rebound involving quiescent lesions and CIRIS, thereby constituting therapeutic and vital challenges.

More recently, it has been demonstrated that patients with milder lymphocytosis after NTZ initiation are more at risk of developing an aggressive disease rebound after NTZ cessation. This adaptive reaction could be mediated by a genetic variant of the Akt protein [8]. A higher risk of clinical relapse or of reactivation seen on MRI has been found after NTZ cessation in patients whose total lymphocyte counts failed to reach 200% of pretreatment values after 6 months of therapy.

In any case, it would be useful to have a diagnostic test that could detect those patients at risk of developing miscellaneous immune reactions during disease-modifying therapy. As NTZ prevents penetration of autoreactive B and T lymphocytes into the CNS, their abnormal survival in the periphery might be involved in disease recurrence or immune reactions after stopping NTZ. Potential associations between human leukocyte antigen (HLA) class I and II alleles and the development of anaphylactic or anaphylactoid reactions in MS patients treated with NTZ also seem feasible. It has been shown that HLA DRB1*13 and 14 alleles are significantly increased in patients who developed anaphylactic or anaphylactoid reactions, whereas HLA DRB1*15 alleles are more often found in patients not suffering such reactions [9].

4. Conclusion

Our present patient presented with several immune manifestations that chronologically coincided with the weeks and months that followed withdrawal of NTZ therapy. While her familial past history could play a role, it is also possible that the NTZ withdrawal was responsible for some of the immune manifestations. As the immune and genetic profiles of patients prone to developing PML emerge, it becomes even more important to identify those patients with a strong propensity for developing autoimmune diseases following the initiation and discontinuation of such therapy.

Disclosure of interest

The authors declare that they have no competing interest.

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