Neurol Sci (2013) 34:2259–2261
DOI 10.1007/s10072-013-1497-3

LETTER TO THE EDITOR

Transient autoimmune hyperthyroidism following the withdrawal of Natalizumab in patients with multiple sclerosis

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Received: 23 January 2013 / Accepted: 27 June 2013 / Published online: 13 August 2013

Keywords Multiple sclerosis · Natalizumab · Autoimmune hyperthyroidism · Thyroid disorders

The treatment of multiple sclerosis (MS) has evolved greatly in recent years with the emergence of new and more effective drugs that have improved the course of the disease. One of these new treatments is Natalizumab (NTZ), a monoclonal antibody that has been highly effective in controlling the disease in aggressive cases. There are no notable adverse effects described but the patients with positive serology for the JC virus can develop progressive multifocal leukoencelophaty (PML). Criteria for risk stratification are currently based on the duration of the treatment and immunosuppressive drugs previously used.

We present two patients who were treated with NTZ and showed a very favorable response excepting that, following withdrawal, both presented a transient autoimmune hyperthyroidism not previously reported.

Case 1 Woman diagnosed with MS in February 2008 at age 23. Patient's mother suffered from thyroid disease. Thyroid hormones tested on diagnosis of the disease and before starting the treatment were normal. In April 2008 she began treatment with subcutaneous interferon beta 1a (IFNβ-1a) and 3 months after the beginning developed an autoimmune subclinical hyperthyroidism (TSH 0.01 mcUI/mL, normal range (NR) 0.34–5.6; TPO-Ab 59.1 UI/mL, NR 0–9; TG-Ab 185–450 UI/mL, NR 0–4). This dysfunction continued during the treatment with IFNβ-1a for 6 months. Due to disease progression in December 2008, the treatment was changed to NTZ with normalization of thyroid hormones and antibodies. These remained normal during the treatment with NTZ for three and a half years and the disease remained stable as well. The patient wanted to get pregnant and therefore the treatment was withdrawn. However in June 2012, 3 months after withdrawal of NTZ, the patient suffered weight loss and general discomfort. The laboratory tests revealed thyroid dysfunction, consistent with autoimmune hyperthyroidism (AIH) (TSH 0.03, TPO-Ab 91.1 and TG-Ab 219.1); however, hyperthyroidism was spontaneously resolved. Because there was an aggravation of the disease and anti-JC virus (JCV) antibodies were negative, in July 2012, treatment with NTZ was resumed and 1 month later, thyroid function returned to normal and remains so to date.

Case 2 Woman diagnosed in October 2009 of MS at the age 26. Sister suffered from hypothyroidism. Thyroid hormones were tested on diagnosis of the disease and results were normal. In February 2010, the patient began treatment with IFNβ-1a, with slight increase of TSH (6.71) consistent with subclinical hypothyroidism but negative antibodies. Due to disease progression, in August 2010, the patient started treatment with NTZ for 18 months and during this period the levels of thyroid hormones and antibodies were normal. NTZ was withdrawn because the test for anti-JCV antibodies in blood resulted positive and the patient decided to abandon treatment. As with the other patient, 3 months following withdrawal of NTZ (April 2012), the patient suffered weight loss and general

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Table 1 Thyroid function at diagnosis, during the treatments and after withdrawal of Natalizumab

	Case 1	Case 2
Age at diagnosis (years)	23	26
Thyroid disease family history	Yes	Yes
First-line therapy	IFN beta 1a	IFN beta 1a
Duration of treatment with NTZ	42 months	18 months
At diagnosis MS	Euthyroid	Euthyroid
During treatment with IFN	Subclinical hyperthyroidism; TSH 0.01 TPO-Ab 59.1 TG-Ab 185–450	Subclinical hypothyroidism; TSH 6.71
During treatment with NTZ	Euthyroid	Euthyroid
Three months after withdrawal of NTZ	Autoimmune hyperthyroidism; TSH 0.03 TPO-Ab 91.1 TG-Ab 219.1	Autoimmune hyperthyroidism; FT4 2.65 TSH 0.08 TPO-Ab 237.5
Posterior check	Euthyroid	Euthyroid

Only abnormal values are reported

Normal values: TSH = 0.34–5.6 mcIU/mL; FT4 = 0.61–1.12 ng/dL; TPO-Ab = 0–9 IU/mL; TG-Ab = 0–4 IU/mL

TSH thyroid-stimulating hormone, *FT4* free thyroxine, *TPO-Ab* antithyroid peroxidase antibody, *TG-Ab* antithyroglobulin antibody

discomfort with evidence of thyroid dysfunction in laboratory tests, consistent with AIH (T4 2.65 ng/dL, NR 0.61–1.12, TSH 0.08, TPO-Ab 237.5 and TG-Ab normal). The clinical and biochemical findings were also self-limited. In July 2012, the patient started treatment with glatiramer acetate and, 1 month later, thyroid function returned to normal and remains so to date.

In summary, we report here two patients, both of whom have a familiar history of thyroid disease and normal basal thyroid profile. Both began IFNβ-1a as first-line therapy, which probably caused a subclinical hyperthyroidism in case 1. Both cases remained euthyroid during treatment with NTZ and 3 months after withdrawal they developed primary AIH spontaneously solved (Table 1).

Following withdrawal, both patients received monthly pulses of intravenous methylprednisolone which may suppress TSH and decrease thyroxine binding globulin (TBG) [1], but does not justify the increase of antibodies or that these alterations emerged after 3 months.

Alternatively, these cases of self-limited AIH may relate to immune reconstitution syndrome (IRS) secondary to the withdrawal of NTZ, which has been previously documented following the start of antiretroviral therapy (ART) in human immunodeficiency virus (HIV)-infected patients [2, 3].

Several studies have analyzed the clinical and radiological consequences on withdrawal of NTZ and its associated IRS, but none of these studies reported significant changes in thyroid function as part of IRS or associated with disease reactivation [4, 5]. Some isolated cases of increased transaminases and bilirubin after the withdrawal of NTZ in patients with prior liver disease have been documented [6].

In a multicenter study in secondary progressive MS (SPMS), IFNβ-1b did not induce thyroid autoantibodies formation [7] but systematic studies on IFNβ-1a are not available.

NTZ acts against the integrin alpha subunit of VLA-4 on the surface of leukocytes, preventing its binding to VCAM-1, involved in mediating immune and inflammatory response. Several studies have suggested that VLA-4 and VCAM-1 pathways could play a relevant role in the autoimmune response in autoimmune thyroid disorders [8, 9].

We suggest that after the withdrawal of NTZ, self-limited autoimmune thyroid disorders may appear as a manifestation of IRS in predisposed people who present or have family members with thyroid disorders or have previously been treated with interferon.

As the use of NTZ seems to control the immune response against the thyroid gland, it could perhaps be interesting to assess its use in other pathologies. In order to corroborate our observations, studies with larger sample sizes are necessary.

We therefore recommend checking systematically thyroid hormones both before and after withdrawal of the drug. In addition to this, it is important to watch for the symptoms that might be associated with such alterations.

Acknowledgments Clara Alfaro-Cervelló, MD, PhD, has contributed in editing the manuscript for non-intellectual content. Pluchino Lab Post doctoral fellow., Dept of Clinical Neurosciences, Cambridge Centre for Brain Repair and Stem Cell Institute, University of Cambridge. Christopher Kellett, Philologist, has contributed in editing the manuscript for non-intellectual content.

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