LETTERS TO THE EDITOR

Autoimmune hyperthyroidism in multiple sclerosis under treatment with glatiramer acetate – a case report

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Dear Sir,

Apart from beta-interferons, Glatiramer acetate (GLAT, Copaxone®), designed to cross-react with myelin basic protein, is the second new drug introduced in MS therapy recently. It seems to have very few side-effects but almost nothing is known about its effect on other autoimmune parameters. We report the case of a 30-year-old female patient who developed relapsing–remitting MS in 1995. GLAT therapy was initiated in an open-label multicentre safety trial. Three years later she complained of palpitations, increased temperature sensitivity, intermittent diarrhoea over a 2-month period and a mild proximal weakness of the legs. She had tachycardia at rest on clinical examination. Electromyogram disclosed myopathic alterations in proximal muscles of the legs. Serologically a diagnosis of immune hyperthyroidism was made. Muscle biopsy showed myopathic changes with storage of Periodic-acid-Schiff-(PAS) positive material consistent with an endocrine myopathy. The patient was put on carbimazole whilst GLAT therapy was continued and her leg weakness improved. Two years after diagnosis, a strumectomy was performed, because of diffuse goitre, to further stabilize the endocrine situation; the neurological situation remained stable.

We cannot exclude a coincidental occurrence of autoimmune phenomena, which are known to occur in up to 1–13.5% of MS patients (DeKeyser, 1988; Seyfert *et al*., 1990; Karini and Abramsky, 1999). Grave's disease was the most common autoimmune finding only in one series, but two out of six patients were clinically silent (Seyfert *et al*., 1990). In most cases, thyroid disease presented as hypothyroidism due to presumed Hashimoto's thyroiditis. Hyperthyroidism was a less common finding in this cohort, which stresses the possible association of our findings with the GLAT treatment. Similarly, elevated thyroidal antibodies have been reported in MS patients taking other immunomodulating agents, i.e. interferon-beta (Schwid *et al*., 1997; Martinelli *et al*., 1998; Durelli *et al*., 1999). GLAT modulates the activity of sensitized T-cells by inducing antigen-specific suppressor cells (Aharoni *et al*., 1998). These cells release T-helper-type-2 (TH-2) cytokines (IL-4, IL-6, IL-10) which may enhance antibody production and the formation of auto-antibodies (Miller *et al*., 1998). T-helper-type-1 (TH-1) cytokines (interferon-gamma, TNF-alpha) are suppressed. The finding of increased serum levels of IL-10 and increased TGF-β and IL-4 mRNA levels in leucocytes of GLAT-treated MS patients (Miller *et al*., 1998) further supports the hypothesis of a TH-2 immune deviation resulting from the therapy. The pathological hallmark in autoimmune hyperthyroidism or Graves' disease are T-helper cells with the cytolytic-suppressive phenotype. Up until now it is not clear whether Grave's disease is a TH-1 or TH-2 mediated illness (Mariotti *et al*., 1991; Roura-Mir *et al*., 1997). Because GLAT induces IL-4, IL-10 and TGF-β, it may induce immune hyperthyroidism. via a TH-2 immune deviation.

Against this background it seems worthwhile to screen for treatable thyroid dysfunction in larger cohorts of naive and GLAT-treated MS. With the knowledge that the relevance of GLAT-induced antibody formation is not yet clear, in our opinion, GLAT therapy could be continued despite the occurrence of Grave's disease.

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