Artículo original

Thyroid disorders in haemophilic patients with chronic hepatitis C (HCV) under Interferon-α (IFN-α) therapy

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Summary

Introduction: Interferon therapy is frequently used for chronic HCV infection. An increased prevalence of thyroid dysfunction and thyroid autoantibodies has been reported with the use of this drug. Objective: Evaluate the overall incidence of thyroid dysfunction in the haemophiliac population under IFN-α treatment for chronic HCV infection. Patients and methods: We retrospectively studied 119 male haemophiliac patients, with chronic hepatitis C treated with IFN-α2a. Results: Negative anti-thyroid antibodies and normal pretreatment thyroid function tests were found in all the patients. Two (0.59%) developed thyroid dysfunction during therapy. Conclusions: In this series, a lower prevalence of thyroid disease was found in the haemophiliac population with chronic hepatitis C receiving IFN therapy (0.59%) compared to the overall thyroid dysfunction described in non-haemophiliac patients.

Key words: *Haemophilia, hepatitis C, interferon- α, thyroid, hypothyroidism.*

Resumen

Disfunción tiroidea en pacientes hemofílicos bajo tratamiento con Interferón - α (IFN-α) por hepatitis C

Antecedentes: El tratamiento con interferón es utilizado con frecuencia en el tratamiento crónico de la infección por el virus de la hepatitis C. El uso de esta droga se acompaña de un aumento en la prevalencia de disfunción tiroidea y auto inmunidad tiroidea. Objetivos: Evaluar la incidencia de disfunción tiroidea en una población de pacientes hemofílicos bajo tratamiento con IFNα por hepatitis C. Pacientes y métodos: Analizamos retrospectivamente la función tiroidea de 119 pacientes hemofílicos tratados crónicamente con IFNα-2a por hepatitis C. Resultados: La función tiroidea fue normal en todos los pacientes antes del tratamiento. Ninguno tenía anticuerpos antitiroideos positivos. Dos pacientes (0.59%) desarrollaron disfunción tiroidea durante el tratamiento. Conclusiones: En esta serie observamos una menor prevalencia de disfunción tiroidea en la población hemofílica bajo tratamiento crónico con interferón por hepatitis C comparado a lo descripto en la población no-hemofílica.

Palabras clave: *hemofilia, hepatitis C, Interferón-α, hipotiroidismo*

Introduction

Interferon therapy is frequently used for chronic HCV infection. The interferons are a group of proteins with antiviral, antiproliferative and immunomodulatory effects. Adverse effects have been recognized with the use of this drug and the development or exacerbation of autoimmune diseases has been reported. An increased prevalence of thyroid dysfunction and thyroid autoantibodies has been reported being the most frequent form of presentation hypothyroidism, which is autolimited in half of the cases.

Chronic HCV patients may show signs of autoimmune phenomena. It has been hypothesized that HCV might share partial sequences with thyroid tissue. HCV may infect thyroid tissue and lead to changes in the structure and immune reaction of the thyroid gland, as sug-

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gested for the high prevalence of thyroid dysfunction in chronic HCV[1].

Haemophilia A and B, X-linked hemorraghic disorders, affect 1 in 5,000 males and 1 in 30,000, respectively[2]. Before the virus-inactivation procedures most patients with haemophilia who were treated with plasma factors became chronically infected with HCV. There are no reports as regards the overall incidence of thyroid dysfunction in the haemophiliac population under IFN-α treatment for chronic HCV infection.

Patients and methods

We retrospectively studied 119 male haemophiliac patients, with chronic hepatitis C defined by the presence of a positive test for anti-HCV antibody (ELISAII or ELISAIII) and HCV RNA positive (nr-PCR) at least in two opportunities in the last six months. All of them were treated with IFN-α2a, 4,5MIU three times for 48 weeks. Thyroid function tests were assessed at the beginning, during and at the end of IFN-α therapy. Serum peripheral levels of TSH, free levothyroxine (T4f), total thyroxine (tT4) and triiodotironine (T3) were measured with standard radioimmunoassay techniques and anti-thyroid antibodies were assessed by hemagglutination assays.

Results

Negative anti-thyroid antibodies and normal pretreatment thyroid function tests were found in all the patients. Two (0.59%) developed thyroid dysfunction during therapy.

Case 1: A 21-year-old man with a history of haemophilia and chronic HCV infection received recombinant IFN-α2a 4.5 MIU thrice weekly during 48 weeks with no thyroid dysfunction. He showed virologic response at the end of treatment (serum HCV RNA undetectable), but after a few weeks it became positive again. 2.5 years later he started a retreatment with IFN-α therapy again and, within 4 weeks, he experienced weight gain, asthenia, constipation, hair loss and edema. A minimally enlarged thyroid gland was found.Thyroid function tests showed: TSH >100 mIU/l (normal range 0.3 to 5.0), total thyroxine (tT4) 3μ/dl (4.5 to 11.0), antimicrosomal antibodies (AMF) 1/102,400, antithyroglobulin (Tgab) 1/100. IFN-α therapy was stopped and he was started on thyroxine. He remains on thyroxine replacement at 150 micrograms daily 3 years later.

Case 2: A 27-year-old man with haemophilia and HCV received IFN-α2a 6 years ago. He had a family history of hypothyroidism. At the 11th month of treatment, he developed: TSH>100, tT4 4.1μ/dl, triiodotironine 35ng/dl, AMF 1/25,600. He was started on thyroxine. When IFN-α was discontinued, he was ran out of thyroxine for evaluation. His thyroid function normalised and AMF became negative.

Discussion

The side effects of IFN therapy appear to be a consequence of immune enhancement or dysregulation state. Thyroid autoimmunity has been widely reported as a side effect of IFN-α treatment with a variable incidence (2.5 to 45.3%)[3-5]. The physiopathological mechanisms of thyroid dysfunction under IFN therapy remain unclear. Burman and col[6] reported during long-term therapy of carcinoid tumors with the human leucocyte-derived IFN-α preparation an increased number of activated T-cells and the expression of HLADR on T-helper and T-suppresor cells in vitro. Besides IFN-α is known to increase MHC class 1 antigen expression on cell membranes[7]. In addition, IFN can affect directly both thyroid hormone sinthesis and secretion *in vitro*[8]. This could explain the occurrence of hypothyroidism in the absence of antithyroid antibodies.

Koh and col[9] reported in a literature review a mean incidence of thyroid dysfunction of 6%, the majority of whom had positive thyroid autoantibodies prior to treatment. A 16% of patients with hypothyroidism induced by IFN did not develop thyroid autoantibodies during treatment suggesting that IFN-α associated thyroid injury may also be mediated by a direct toxic mechanism.

Imagawa and col[10] found a higher prevalence of thyroid dysfunction in patients with chronic HCV compared with those with HBV before and in the end of IFN- therapy. Conversely, Betterle and col[11] did not find an increased prevalence of thyroid autoantibodies in 70 patients with HCV chronic infection before IFN-α therapy compared with control subjects.

Marazuela and col[1] have not found an increa-

sed prevalence of thyroid dysfunction before IFN-α treatment in a series of 207 patients with HCV. During IFN-α therapy 14.8% of female patients (5.5% of all treated patients) without previous thyroid abnormalities developed thyroid dysfunction.

Taking into consideration the incidence of thyroid dysfunction during IFN-α treatment, it has been suggested that all patients receiving IFN-α therapy should have their thyroid function assessed before, during and for at least 6 months after IFN-α has been stopped[9].

Between 60 to 95% of haemophiliac patients have HCV infection. In this series, a lower prevalence of thyroid disease was found in the haemophiliac population with chronic hepatitis C receiving IFN therapy (0.59%) compared to the overall thyroid dysfunction described in non-haemophiliac patients. Moreover, no prevalence of thyroid dysfunction or autoimmunity was detected basally in the haemophiliac patients, being significantly different with the prevalence of hypothyroidism of 2.5% and of positive thyroid autoimmunity of 10% which has been reported in a group of 40 healthy individuals who attended the blood bank of our hospital[12]. The repeated administration of large amounts of blood products is thought to induce a subclinical immunodeficiency state. The extent of these abnormalities correlates to the amount of concentrated factor VIII administered. We can speculate that this state of immunosuppression is the reason for the lower prevalence of autoimmune thyroid disease.

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