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 haemophilic population under IFN-α treatment for chronic HCV infection. Patients and methods: We retrospectively studied 119 male haemophilic 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 haemophilic population with chronic hepatitis C receiving IFN therapy (0.59%) compared to the overall thyroid dysfunction described in non-haemophilic patients.

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

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-
gested for the high prevalence of thyroid dys-
function in chronic HCV1.

Haemophilia A and B, X-linked hemorrhagic
disorders, affect 1 in 5,000 males and 1 in
30,000, respectively2. Before the virus-inactiva-
tion procedures most patients with haemophilia
who were treated with plasma factors became
chronically infected with HCV. There are no re-
ports as regards the overall incidence of thyroid
dysfunction in the haemophiliac population un-
der IFN-α treatment for chronic HCV infection.

Patients and methods

We retrospectively studied 119 male haemo-
philiac patients, with chronic hepatitis C defined
by the presence of a positive test for anti-HCV
antibody (ELISAII or ELISAIII) and HCV RNA po-
sitive (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 ther-
apy. Serum peripheral levels of TSH, free levo-
thyroxine (T4f), total thyroxine (tT4) and triiodo-
tironine (T3) were measured with standard ra-
dioimmunoassay 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 recei-
ved recombinant IFN-α2a 4.5 MIU thrice weekly
during 48 weeks with no thyroid dysfunction. He
showed virologic response at the end of treat-
ment (serum HCV RNA undetectable), but after
a few weeks it became positive again. 2.5 years
later he started a retreatment with IFN-α ther-
apy 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 antibo-
dies (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 4.1 µ/dl, triiodotironine 35ng/ml, 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 dys-
regulation state. Thyroid autoimmunity has been
widely reported as a side effect of IFN-α treat-
ment with a variable incidence (2.5 to 45.3%)35.
The physiopathological mechanisms of thyroid
dysfunction under IFN therapy remain unclear.
Burman and col6 reported during long-term the-
rapy of carcinoid tumors with the human leuco-
cyte-derived IFN-α preparation an increased
number of activated T-cells and the expression
of HLADR on T-helper and T-suppressor cells in
vitro. Besides IFN-α is known to increase MHC
class 1 antigen expression on cell membranes7.
In addition, IFN can affect directly both thyroid
hormone sinthesis and secretion in vitro8. This
could explain the occurrence of hypothyroidism
in the absence of antithyroid antibodies.

Koh and col9 reported in a literature review a
mean incidence of thyroid dysfunction of 6%,
the majority of whom had positive thyroid au-
toantibodies prior to treatment. A 16% of patients
with hypothyroidism induced by IFN did not de-
velop thyroid antibodies in the absence of IFN-α
associated thyroid injury may also be mediated by a direct toxic mecha-
nism.

Imagawa and col10 found a higher prevalen-
ce of thyroid dysfunction in patients with chron-
ic HCV compared with those with HBV before
and in the end of IFN- therapy. Conversely, Bet-
terle and col11 did not find an increased preva-
ience of thyroid autoantibodies in 70 patients with
HCV chronic infection before IFN-α therapy com-
pared with control subjects.

Marazuela and col12 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.

**Bibliografía**