Role of thyroid scan in diagnosis of interferon induced thyroid dysfunction

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Abstract

The study included 80 HCV Egyptians patients eligible for treatment with interferon alpha.

Thyroid hormones, thyroid autoantibodies (anti TG Ab, anti-peroxidase Ab and anti TSH Ab), thyroid uptake and scan were performed at basal condition and 3 months after treatment.

After 3 months of IFN-α administration, 23/80 patients (28.7%) developed thyroid dysfunction.

A statistically significant elevation of thyroid autoantibodies was detected in 58%of patients compared to 36% at basal condition. Do novo thyroid autoimmunity was detected in 22.5% of patients.

Key Words : thyroid scan - interferon - thyroid dysfunctions.

List of contents

Introduction..... 1

Aim of the work 4

Review of literature

- Physiology of thyroid gland 5
- Hepatitis c & Interferon 14
- Predisposition to interferon induced thyroid dysfunctions 22
- Interferon induced thyroid dysfunctions.. 26
- Mechanism of interferon induced thyroid dysfunctions 34
- Diagnosis & treatment of interferon induced thyroid dysfunctions 39

Patient and method 48

Result 53

Case presentation 68

Discussion 71

Conclusion and recommendations..... 79

Summary.....81

References 83

Arabic summary 98

List of tables

Tables	Description	Page
Table1	Normal values of thyroid hormones and anti-thyroid antibodies	50
Table2	Age and sex distribution among normal, toxic and thyroiditis groups.	55
Table3	Thyroid hormonal profile changes at base line and 3months after IF-αtreatment in the studied groups with comparison.	57
Table4	Thyroid uptake changes at base line and 3 months after IF-αtreatment in the studied groups with comparison.	59
Table5	Prevalence of HCV patients with elevated anti-thyroid antibodies at basal condition and after 3 months.	61
Table6	Mean values of anti-thyroid antibodies at basal condition and after 3 months	61

List of Figures

Figure	Description	Page
Figure1	Direct Effects of IFNα on the Thyroid	37
Figure2	Immune Mediated Effects of IFNα	38
Figure3&4	Treatment of interferon induced thyroid Dysfunction	47
Figure5	Prevalence of thyroid dysfunction3 months after IF-α therapy	55
Figure6	Thyroid uptake values before and after treatment in the studied groups	59
Figure7	Serum anti TG Ab changes before and after IF-α treatment in the studied groups.	65
Figure8	Serum anti-peroxidase Ab changes before and after IF-α treatment in the studied groups	65
Figure9	Serum anti-TSH Ab changes before and after IF-α treatment in the studied groups	65
Figure10	Correlation between Thyroid scan uptake value and Anti TSH Ab after 3 months of IF-α therapy	67

List of Abbreviations

AITD	Autoimmune induced thyroid dysfunctions
cAMP	Cyclic adenosine monophosphate
DIT	Diiodotyrosin
ds RNA	Double strand RNA
ELISA	Enzyme-linked immunosorbant assay
GAS	Gene transcription by binding to interferon activated site
GD	Graves ' disease
G protein	Guanine nucleotide binding protein
HCG	Human chorionic gonadotropin
HT	Hashimoto's Thyroiditis
IFN	Interferon
IFNAR	Interferon alpha receptors
IIT	Interferon induced thyroiditis
IL	interleukin
INR	International normalized ratio
ISGs	Interferon stimulated genes
ISGF3	Interferon stimulated genes factor 3
ISREs	Interferon stimulated response elements
JAK-STAT	Janus kinase - STAT
MDA5	Melanoma differentiation antigen 5
MHC	Major histocompatibility complex
MIT	Monoiodotyrosin
MTC	Medullary thyroid carcinoma
NIS	Sodium iodide symporter
NK cells	Natural killer cells
PCR	Polymerase chain reaction

RIG	Retinoic acid inducible gene
STAT	Signal transducer and activator of transcription
TAb	Thyroid antibodies
TG	Thyroglobulin
TG-Ab	Thyroglobulin antibodies
Th cells	T – helper cells
TLR3	Toll like receptor 3
TPO-Ab	Thyroid peroxidase antibodies
TR	Thyroid hormone receptors
TR-Ab	Thyrotrophin receptor antibodies
TRH	Thyrotroponin releasing hormone
TSH	Thyroid stimulating hormone
TSHR	Thyroid stimulating hormone receptor

INTRODUCTION

Hepatitis C is an infectious disease affecting primarily the liver, caused by HCV. The infection is often asymptomatic, but chronic infection can lead to scarring of the liver and ultimately to cirrhosis, which is generally apparent after many years. In some cases, those with cirrhosis will go on to develop liver failure, liver cancer or life-threatening esophageal and gastric varices. HCV is spread primarily by blood-to-blood contact associated with intravenous drug use, poorly sterilized medical equipment and transfusions (1).

Interferon was discovered almost 50 years ago by **Isaacs and Lindenmann** who observed that virus-infected cultures produced a protein that reacted with cells, making them resistant to infection by many other viruses (2).

Interferon-α (IFNα) was the first cytokine to be reproduced by recombinant DNA technology and has emerged as a major therapeutic modality for several malignant and nonmalignant diseases. Among the diseases treated by IFNα are melanoma, renal cell carcinoma, hairy cell leukemia, Kaposi's sarcoma, hepatitis B and C. However, the most common prescription for IFNα treatment is hepatitis C (3).

IFNα therapy is associated with many side effects ranging from influenza-like symptoms to hematologic and neuropsychiatric side effects (4).

One of the commonest side effects of IFNα therapy is thyroiditis, with up to 40% of HCV patients on IFNα developing clinical or subclinical disease. In some cases interferon induced thyroiditis (IIT) may result in severe symptomatology that may necessitate discontinuation of therapy. IIT can be classified as autoimmune type and non-autoimmune type. Autoimmune IIT may manifest by the development of thyroid antibodies without clinical disease, or by clinical disease which includes both autoimmune hypothyroidism (Hashimoto's thyroiditis) and autoimmune thyrotoxicosis (Graves' disease). Non-autoimmune thyroiditis can manifest as destructive thyroiditis, with early thyrotoxicosis and later hypothyroidism, or as non-autoimmune hypothyroidism (5).

Therefore, current treatment algorithms recommend that HCV patients receiving IFNa therapy undergo periodic thyroid function testing throughout their treatment course (6).

The fact that only 20-40% of HCV patients receiving IFNa therapy develop IIT suggests that HCV and IFNa act synergistically to induce thyroid disease in genetically

predisposed individuals. Therefore, it is hypothesized that genetic susceptibility plays a major role in the etiology of interferon induced thyroiditis (5).

AIM OF THE WORK

The aim of the current work is to:

- Assess the value of thyroid scan in diagnosis of interferon-induced thyroid dysfunction.

- Estimate the frequency of thyroid dysfunction in patients under interferon therapy.

- Predict patients who will be at risk to develop thyroid dysfunction during the course of treatment with Interferon.

PHYSIOLOGY OF THE THYROID GLAND

The thyroid gland weighs 10 to 20 g in normal adults and is responsible for the production of two families of metabolic hormones, the thyroid hormones, thyroxine (T4) and triiodo-thyronine (T3) and calcium-regulating hormone (calcitonin). The spherical thyroid follicular unit is the important site of thyroid hormone production which is made up of a single layer of cuboidal follicular cells that encompass a central depository of colloid filled mostly with thyroglobulin (TG), the protein in which T4 and T3 are synthesized and stored(7).

Iodine Metabolism

Iodine is essential for the production of thyroid hormones. It can be efficiently absorbed from the gastrointestinal (GI) tract in the form of inorganic iodide and rapidly enters the extracellular iodide pool. The thyroid gland is responsible for storing 90% of total body iodide at any given time, with less than 10% existing in the extracellular pool. Iodide is stored in the thyroid as preformed thyroid hormone or as an iodinated amino acid (8).

Iodide is transported from the extracellular space into the follicular cells against a chemical and electrical gradient via an intrinsic transmembrane protein located in the basolateral mem-

brane of the thyroid follicular cells. Once inside the cells; iodide rapidly diffuses to the apical surface, where it is quickly moved to exocytic vesicles. Here, it is rapidly oxidized and bound to TG. Transport of iodide into follicular cells is regulated by thyroid-stimulating hormone (TSH) from the pituitary gland, as well as by the follicular content of iodide (8).

Thyroid Hormone Synthesis

Once organic iodide is efficiently oxidized and bound, it couples to TG with tyrosine moieties to form iodotyrosines in a single conformation (monoiodotyrosine [MIT]) or a coupled conformation (diiodotyrosine [DIT]). The formation of DIT and MIT is dependent on an important intracellular catalytic agent, thyroid peroxidase, which has been well characterized and is an integral part of the initial process of organification and storage of inorganic iodide. This enzyme, along with TG, is remarkably specific to the thyroid follicular cells, making both important in the diagnosis and management of autoimmune thyroid disease and well-differentiated thyroid cancer (9).

MIT and DIT are biologically inert. Coupling of these two residues gives rise to the two biologically active thyroid hormones, T4 and T3. T4 is formed by the coupling of two molecules of DIT, whereas T3 is formed by the coupling of one molecule of MIT with

one molecule of DIT. In normal circumstances, formation of T4 predominates (9).

Both T3 and T4 are bound to TG and stored in the colloid in the center of the follicular unit, which allows quicker secretion of the hormones than if they had to be synthesized de novo. This rapid and metabolically active process normally results in the storage of about 2 weeks' worth of thyroid hormone in the organism under normal circumstances. T4 is the most thyroid hormone released from the thyroid gland, which is deiodinated in peripheral extrathyroidal tissues and converted to T3 (9).

Release of T4 and T3 is regulated by the apical membrane of the follicular cell via lysosomal hydrolysis of the colloid that contains the Tg-bound hormones. The apical membrane of the thyroid cell forms multiple pseudopodia and incorporates TG into small vesicles, which are then brought into the cell apparatus (9).

Within the vesicles, lysosomal hydrolysis results in the reduction of the disulfide bonds and T3 and T4 are then free to pass through the basement membrane and be absorbed into the circulation, where more than 99% of each hormone is bound to serum proteins. This metabolic process is efficient in releasing T3 and T4 while maintaining the storage components, TG and colloid, within the follicular apparatus (9).