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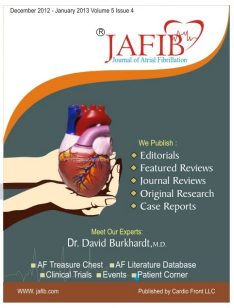

Subclinical Hypothyroidism: An Overlooked Cause of Atrial Fibrillation?

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Introduction

The association between clinical[1] or subclinical[2] hyperthyroidism and atrial fibrillation is established from large prospective cohort studies, with serum free thyroxin (T4) concentrations correlating with atrial fibrillation rates.[3] However, the role of subclinical hypothyroidism as a causal factor for atrial fibrillation has not been elucidated.

Recently, we have had under our care two patients with episodes of paroxysmal or persistent atrial fibrillation and absence of identifiable causes, other than subclinical hypothyroidism.

The first patient, a 42-year-old female presented with frequent palpitations, corresponding to brief episodes of non-sustained, paroxysmal atrial fibrillation on 24- hour Holter recordings. Hypertension was excluded, based on repeated blood pressure recordings and on ambulatory monitoring; echocardiography, exercise stress testing, as well as blood biochemistry were normal. However, mild subclinical hypothyroidism was diagnosed based on thyrotropin (thyroid-stimulating hormone, TSH) values of 5.69mIU/L, with normal triiodothyronine(T3) (1.53ng/ml, laboratory reference values: 0.56-1.56ng/ml) and free(T4) (1.12ng/dl, laboratory reference values: 0.6-1.37ng/dl) values. She was treated with levothyroxin 50ug daily and her symptoms progressively resolved; during a 24-month follow-up, thyroid function tests remained normal and she had no further episodes of atrial fibrillation, either clinically or on repeated 24-hour Holter recordings.

The second patient, a 45-year-old male, presented with persistent atrial fibrillation, which was cardioverted to sinus rhythm, after failure of pharmacologic treatment with oral propafenone and intravenous amiodarone. He gave a history of autoimmune (Hashimoto) thyroiditis associated with positive antithyroid peroxidase antibodies (40.5IU/ml, laboratory reference values: <9IU/ml). As in the first case, meticulous investigation was normal, apart from thyroid function tests. Despite previous normal thyroid function tests (4 years prior to the index evaluation), subclinical hypothyroidism was diagnosed, based on TSH values of 7.67mIU/L, with normal T3 (0.96ng/ml) and free T4 (0.68ng/dl). During the subsequent 6 months, he had three more episodes of persistent atrial fibrillation, despite levothyroxin 50ug daily and antiarrhythmic treatment, initially with sotalol 80mg t.i.d. and subsequently with propafenone 150mg t.i.d.; at that time, thyroid function tests had improved but were still abnormal, with TSH values of 5.36mIU/L, whereas T3 (0.80ng/ml) and free T4 (0.72ng/dl) remained within normal range. Levothyroxin was increased to 100μg daily, which normalized TSH values to 2.48mIU/L after 6 months, again with normal T3 (0.85ng/ml) and free T4 (1.00ng/dl) levels. During a further 12-month follow-up, only brief episodes

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of paroxysmal atrial fibrillation were noted on repeated 24-hour Holter recordings.

Our two case-studies indicate a possible causal relationship between subclinical hypothyroidism and atrial fibrillation. This notion is further supported by three important pieces of evidence in the literature:

(a) The effects of subclinical hypothyroidism was examined during the immediate post-operative period in patients undergoing coronary artery bypass grafting[4], a well described risk factor for atrial fibrillation; in this study,[4] 224 patients with normal thyroid function and 36 patients with subclinical hypothyroidism were enrolled. Although there were no significant differences in major adverse cardiovascular events, patients with subclinical hypothyroidism had a higher incidence of postoperative atrial fibrillation (with an odds ratio of 2.55) than those with normal thyroid function; this differences was statistically significant, even when corrected for known risk factors, such as age, gender, body mass index, emergency operation, use of cardiopulmonary bypass, combined valvular operation, preoperative creatinine levels, left ventricular systolic dysfunction and non-use of β-blockers.

(b) An earlier prospective cohort study[5] included approximately 2000 clinically and biochemically euthyroid subjects over 60 years of age, who were followed for 10 years; this study[5] reported a three-fold relative risk of atrial fibrillation in subclinical hyperthyroidism and TSH values below 0.1mIU/L. However, an additional finding was a trend towards higher incidence (12.5% versus 8.4%) of atrial fibrillation in subjects with subclinical hypothyroidism (TSH values >5mIU/L) compared to those with normal TSH values (0.4-5.0mIU/L); this rate (12.5%) was almost identical to the atrial fibrillation rate (12.2%) observed in subjects with subclinical hyperthyroidism and TSH values between 0.1 and 0.4mIU/L.[5]

The importance of subclinical thyroid dysfunction on cardiovascular disease was recently highlighted in a pooled analysis of data from 6 prospective cohort studies, including over 25000 participants,[6] of whom 8.1% had subclinical hypothyroidism (defined as TSH levels greater than 4.5mIU/L) and 2.6% had subclinical hyperthyroidism (defined as TSH levels below 0.45mIU/L); during follow-up, an increased risk for heart failure was found for high and low TSH levels, particularly for values above 10mIU/L and below 0.10mIU/L. (c) The mechanism of atrial fibrillation in subclinical hypothyroidism is complex and likely multifaceted. Slowed myocardial relaxation and impaired ventricular filling have been consistently shown in patients with subclinical hypothyroidism;[7] thus, abnormal left ventricular diastolic function increases left atrial pressure and can result in stretch-induced atrial tachyarrhythmias. In addition, several lines of evidence have linked subclinical hypothyroidism with coronary artery disease, which, in turn, is associated with atrial fibrillation. To this end, subclinical hypothyroidism increases arterial stiffness,[8] an important risk factor for atherosclerotic heart disease. Furthermore, patients with subclinical hypothyroidism exhibit more prominent atherogenic parameters, such as low-density-lipoprotein cholesterol and lipoprotein(a) .[9]

A recent experimental study,[10] added important information on the potential mechanisms of atrial fibrillation in subclinical hypothyroidism. In hyperthyroid rats, the expression of L-type calcium channel α-subunit was reduced in vivo by ~60%, but a (statistically significant) reduction (by ~35%) was found also in hypothyroid animals. More importantly, hypothyroid - but not hyperthyroid - rats had enhanced collagen expression in the atrial myocardium [10], indicating additional structural remodeling.

In addition to these considerations, we offer the following possible explanation: subclinical hypothyroidism is a compensated state, during which the rise in TSH attempts to maintain thyroid economy by converting T4 to the more metabolically- active T3. Thus, at this transient stage, higher T3/T4 ratio may provide the milieu for 'cardiac T3-thyrotoxicosis'. Data favoring this notion stem from an previous study,[11] in which serum free thyroid hormones were measured in patients at different stages of hypothyroidism. A progressive decrease of free T4 levels was reported, along with a corresponding increase of TSH levels, from healthy subjects to subclinical, mild and severe hypothyroids; however, the decrease in free T3 levels was less prominent in subclinical and mild hypothyroidism, with free T4 being the most useful

discriminating variable between groups. The importance of subtle alterations in thyroid hormones in atrial arrhythmogenesis is further supported by the findings of a large population-based observational study,[3] which showed that circulating T4 levels are related to atrial fibrillation, even in patients with values well within normal range. Thyroid receptors play a critical role in mediating the diverse actions of thyroid hormones[12] and constitute a potentially important parameter that should be taken into account. Indeed, thyroid hormone signaling is altered in response to various stresses, producing local myocardial alterations in the homeostasis of thyroid hormones.[13] For example, significant alterations in thyroid hormone signaling have been demonstrated in the post-myocardial infarction setting; a recent experimental study[13] showed thyroid receptor-alpha-1 down-regulation, resulting in tissue hypothyroidism, with unchanged circulating T4 and T3 levels. These results may fuel future research on the possible relationship between altered thyroid hormone signaling and atrial arrhythmogenesis in the setting of subclinical hypothyroidism.

Conclusions

There is evidence that subclinical hypothyroidism may be a risk factor for atrial fibrillation. Prospective cohort studies are required, directly examining the potential association between these two disease entities; likewise,their pathophysiologic link should be further explored at basic and clinical level.

Disclosures

No disclosures relevant to this article were made by the authors.

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