

Cardiothyreosis: Pathogenic Conjectures, Clinical Aspects and Surgical Approach

M.R. Diaconescu¹, I. Costea¹, M. Glod¹, S. Diaconescu²

¹IVth Surgical Department, "Gr T Popa" University of Medicine and Pharmacy Iași, Romania

²Vth Pediatric Department, "Gr T Popa" University of Medicine and Pharmacy Iași, Romania

Rezumat

Cardiotireozele: conexiuni patogenice, aspecte clinice și indicații chirurgicale

Introducere: Prezența manifestărilor cardiovasculare a fost semnalată odată cu primele cazuri de hipertiroidism descrise de Parry (1825) și Basedow (1840) fiind menționată de ultimul autor în clasică triadă de la Merseburg. Componenta cardiacă poate fi genuină sau se instalează ca o complicație a unei suferințe preexistente.

Material și metodă: Autorii prezintă 49 observații de cardiotireoze: 11 bărbați și 38 femei în vârstă de 12-72 (medie 45) ani, selectate dintr-o serie omogenă de 138 tirotxicoze operate în cursul a două decenii. Au fost înregistrate 15 cazuri de boală Basedow, 16 adenoame toxice și respectiv 18 guși multinodulare toxice. În cadrul acestora s-au asociat - sub formă izolată sau dominantă clinic - insuficiență cardiacă în 10 cazuri, tulburări de ritm în 21 situații și suferințe coronariene la 9 pacienți. Acestora li s-au adăugat 7 cazuri de hipertensiune arterială și alte două prezentând valvulopatii mitrale. Majoritatea observațiilor a realizat însă asocieri ale acestor suferințe. În cazul hipertiroidismului diagnosticul a fost stabilit clinic fiind confirmat de examenele imagistice și dozările biologice în timp ce suferințele cardiace au fost certificate prin anamneză, examen obiectiv, EKG și ecocardiografie. Toate cazurile au fost operate practicându-se 33 tiroidectomii totale și aproape totale și 16 lobectomii fără a se înregistra complicații cu excepția a trei

episoade de tahiaritmie postoperatorie, în rest obținându-se vindecări sau ameliorări semnificative în 43 (87,7%) din cazuri. **Discuții și concluzii:** Diagnosticul patogenic al așa ziselor cardiotireoze nu este întotdeauna ușor de formulat, în special datorită componentei cardiace care poate "umbri" o suferință sub-clinică, mascată a hipertiroidismului, uneori produs de condiții etiologice inedite (administrare de amiodaronă). Tratatamentul medicamentos al acestor condiții realizează doar ameliorări instabile și tranzitorii fiind necesare metode radicale de eliminare a parenchimului glandular pathologic fie prin administrarea de I 131, preferată în numeroase centre fie prin exereze chirurgicale bine pregătite și executate, eficiente mai ales în tiromegaliile importante și adenomul toxic.

Cuvinte cheie: cardiotireoze, hipertiroidism, insuficiență cardiacă, aritmie, tiroidectomie

Abstract

Introduction: The presence of striking cardiovascular manifestations were noted in the first descriptions of hyperthyroidism owing to Parry (1825) and Basedow (1840) in his famous Merseburg triad. Hyperthyroidism may either cause cardiac complications in individuals with a normal myocardium (genuine form of disorder) or complicate preexisting cardiac troubles.

Material and method: An homogenous series of 49 cardiothyreosis, 11 males and 38 females, aged 12 - 78 (mean 45) years selected between 138 thyrotoxic patients operated on in a period of two decades is herein presented. There were registered 15 Basedow diseases, 16 toxic adenomas and 18 multinodular toxic goiters. Among these were found isolated or dominating when combined together, 21 cases with rhythm troubles (4 with

Corresponding author:

Mihai Glod, MD
no 1, Ibrăileanu Str, 700506 Iași, Romania
E mail: mihai_glod@yahoo.com

extrasystolic arrhythmia and one with fibrilloflutter, 10 cases with cardiac failure and 9 cases with coronary cardiac disease. To these 7 hypertensive patients and two with mitral valvulopathy were added. In hyperthyroidism clinical diagnosis was confirmed on imaging exams and hormonal determinations while cardiovascular disturbances was ascertained by interrogatory, clinical signs, EKG and echocardiography. All our cases were operated on performing 33 total or near total thyroidectomies and 16 lobectomies without morbidity recording however 5 postoperative tachyarrhythmias but finally most of them with good clinical results (87,7% cured or significantly ameliorated).

Discussions and conclusions: Pathogenic diagnosis of such so-called "cor thyreotoxicosis" is not always easy on account of cardiovascular syndrome which frequently overshadowed the thyroid subclinical pictures or emergencies of new described entities as amiodarone induced thyrotoxicosis. The single administration of a whole calculated dose of I 131 with subsequent treatment with thyrostatics and β -blockers till remission of toxicosis is achieved can be chosen opposing to thyroidectomy after short medicamentous preparation which is effective in large thyromegalias and toxic adenomas.

Key words: cardiomyopathy, hyperparathyroidism, cardiac failure, arrhythmia, thyroidectomy

Introduction

Relations between thyroid and myocardium debuting in ontogenesis are dominated by cardiovascular troubles in hyperthyroidism mentioned from the initial descriptions of Parry (1825) whose patient dies by heart failure and also in Basedow's classic Merseburg triad (1840). (1,2)

Many subsequent authors as Dunhill (1909), Hamilton (1924), Levine and Sturges (1924), Lahey (1929), Colson and Berard (1934) - which proposed the term of cardiomyopathy - and Hertzler (1944) that of cardiotoxic goiter, described the concurrent presence of a heart trouble i.e. heart congestive failure, tachyarrhythmia and coronary heart disease in cases with overt or masked (apathetic) hyperthyroidism. (3,4,5,6,7,8,9,10). In our country have published studies in this domain signed by Caloghera (1968), Popovici (1991), Diaconescu (1993). (11,12,13,)

The frequency of cardiomyopathy is extremely variable being taken in consideration by the obviousness and intensity of toxic syndrome, a variety of heart troubles and its isolated or associated character. Heulin (1983) estimate the incidence of these condition in very large limits situating it between 10-60% of hyperthyroid patients, occurring preferentially in the 5th and 6th decades of age and with a higher proportion of men than in usual thyrotoxicosis. (14,15,16,17,18,)

The nosologic setting of cardiomyopathy is still under discussion, traditional authors enclosing in various denominations

(hyperthyroid heart, cardiotoxic goiter, thyrotoxic cardiomyopathy, cor thyrotoxicum etc) only hyperthyroid patients accompanied by complete arrhythmias and/or cardiac insufficiency with an normal preexisting myocardium and which demonstrate total reversibility of condition after therapy. (4,6,7,9,19,20,21,22,23)

Conversely, another authorities rallies in this group all cardiovascular manifestations described in thyrotoxic patients whatever of a determined etiology i.e. congenital, rheumatic, hypertensive, atherosclerotic or pulmonary and those in which there is no other identifiable cause except thyroid hyperfunction. (5,8,24,25,26,27)

Difference between these two clinicopathogenical categories is not always easy to assign.

Material and Methods

A personal series of 49 thyrocardiac patients, 11 males and 38 females (R: 1/3,5), aged between 12-78 (mean) 45 years was selected between 136 thyrotoxic cases operated on over a period of two decades is retrospectively presented. There were registered 15 Basedow's diseases, 16 toxic adenomas (TA) and 18 multinodular toxic goiters (MNTG), clinically diagnosed and confirmed by imaging and hormonal exams. The main prevalent or isolated cardiovascular clinical pictures was represented by 10 cases of cardiac failure, 21 cases of marked rhythm troubles and 9 cases of coronary heart disease to which 7 hypertensive and respectively two patients associating mitral valvulopathies were added. In all of these diagnosis was assigned by anamnesis, physical examination, EKG and echocardiography. All cases were operated on performing 33 total or near total thyroidectomies in bilateral lesions and 16 lobectomies in toxic adenomas. Careful indications of surgical treatment and preoperative preparation fulfilled by an accurate technique, conducted outside cure of all operated hyperthyroid patients to good results of cardiac features obtaining complete recession or substantial improvement in 87,7% (43/49) observations.

Patients study design

In our series is retrieved characteristic female predominance of thyroid pathology, particularly in thyrotoxicosis (38/11, R=3,4/1) but the superior overall frequency of male cases in hyperthyroid heart diseases emphasis the higher severity of those endocrine conditions in this sex. Age limits ranging between 12-78 (mean 45) being on average 5,5 years older than those registered in our cases of hyperthyroidism, interesting especially the 4th and 5th decades. Distribution of cases by age group must be correlated however with the clinical variety of patients with hyperthyroidism.

Most cases under 40 years was represented by patients with florid Basedow's disease showing rhythm troubles, increases of blood tension, and moderate coronary features - generally reversible - while older age groups include severe forms of cardiovascular sufferings i.e. atrial fibrillation, myocardial ischemia and consecutive heart failure described in carriers of TA and MNTG with long evolution. Even if ultimately are

achieved similar clinical aspects could however be distinguished primary cardiomyopathy installed in a previous anatomically and functionally normal heart, which are usually reversible after treatment of thyrotoxicosis. These conditions intervene in both the genesis and aggravation of cardiovascular phenomenon. They may be opposed to many cases with long standing (multi)nodular goiters and latent or frust toxic syndrome (apathetic borderline hyperthyroidism), more or less treated in time, which subject the patient to an excessive cardiocirculatory effort that end in acute accidents or chronic decompensated heart failure.

Clinical cardiovascular aspects

Mains clinical aspects are mentioned in the *Table 1* noting that for inclusion in a specific nosological category, we considered patients in which the cardiac trouble has an isolated or dominant presentation. However in most situations we noticed coexistence in the same case of impressive arrhythmia disturbance or angor pectoris and/or excessive values of blood pressure, each of them prevailing clinical scene but ultimately all leading to a global deterioration of myocardial functions.

Rhythm troubles registered in 21 cases representing 42,8% of total numbers of thyrocardiac patients and respectively 13,9% from all the cases of hyperthyroidism.

- extrasystolic arrhythmias 4 cases – atrial, ventricular or mixed – of which 3 were isolated, did not put special problems of diagnosis and therapy, they generally belonging to uncomplicating thyrocardiac conditions.
- tachyarrhythmias by auricular fibrillation (almost always supraventricular) was the commonest complication of hyperthyroidism. Isolated form was present in 5 cases being accompanied usually by functional symptoms as palpitations, precordial discomfort and dyspnea. The EKG strikes anarchic character of cardiac revolutions, absence of P waves traducing the disparition of atrial systoles contrasting with the almost normal aspect of ventricular complexes. Repolarisation disorders encountered two cases is due to either to the accelerate ventricular rate – 100 b/min or a coexisting myocardial suffering.

Arrhythmia was characterized by outstanding resistance to tonicardiac drugs (their metabolism being accelerated by hyperthyroidism) contrasting with encouraging efficacy of β -blockers. Less effective treatment allows evolution to heart decompensation in two patients.

Spectacular restoration of cardiac rhythm was obtained in 9 of 14 cases undergoing surgery. The other patients recoured

successfully to electrically defibrillation or medical therapy. Only in one case (BM., 58 yr toxic adenoma) with auricular flutter with 2/1 atrioventricular production was performed a lobectomy after oral β -blockade and direct cardioversion with reverted the patient to normal sinus rhythm and euthyroidism. We mentioned also in our series two patients with postoperative tachyarrhythmia with clinical and EKG aspect of complete fibrillation, salient by the rapidity and irregularity of pulse. Both were favourably influenced by the administration of antiarrhythmic medication.

Although fortunately we have not met thyrotoxic crisis in the last years, severe rhythm troubles may precede or add to the clinical picture of this serious postoperative complication. Congestive heart failure - 10 cases (20,4%) - constituted the major complication and the final term of neglected thyrocardiac disease. In 9 cases cardiac insufficiency was associated with a severe arrhythmia and/or secondary coronary heart disease and one patient coexisted with a mitral stenosis. Most of them could not be established a clear sequence of events and correlation between history of thyrotoxic manifestations and myocardic sufferings. Also many patients were hospitalised for long periods in medical clinics and treated by “refractory” heart failure before a careful clinical examination revealed the presence of goiter.

Seven subjects exceeded 50 years and half of them belonging to nodular thyrotoxicosis. This require that in the advent of cardiac failure installed around this age without any apparent cause and ineffective to the standard therapy, the possibility of hyperthyroidism must be evoked.

The distribution of our heart patients according to the NYHA functional classification were 3, 4 and 3 cases for NYHA classes II, III and IV respectively.

Cardiac weakness in thyrotoxic patients cumulated common manifestations i.e. palpitations, exertional dyspnea, precordial pains, cyanosis, painful hepatomegaly, hepatojugular reflux, distal edema, oliguria, raised venous pressure, weight loss etc. We also noted as peculiar features of this complication the increased circulatory velocity and moderate cardiomegaly disproportionate with clinical picture.

Remembering the most important trait of this distress appearing in hyperthyroid individuals was the tenacious resistance to therapy usually effective in heart failure with another etiologies or on different medical support. Confirmed patients with heart failure significantly selected the surgical indication, formulated only in few situations after a long, tedious and not always complete compensation. However we noticed three cases with complete disappearance of the main

Table 1. Isolated or main dominating clinical aspects described in our series of 49 thyrotoxicosis

Cardiomyopathy/ Hyperthyroidism		Extrasystolic arrhythmia	Auricular fibrillation	Fibrillo flutter	Postoperative arrhythmia	Cardiac failure	Angor pectoris	High blood pressure	Other*
TOTAL	49 (34,5%)	4	14	1	2	10	9	7	2
Basedow	15	2	4	-	-	3	3	2	1
Toxic adenoma	16	1	6	1	1	3	2	2	-
MNTG	18	1	4	-	1	4	4	3	1

complaints while a more or less alleviation was considered in the other patients.

Hyperthyroidism appeared also as a causative or precipitating factor of coronary heart disease, particularly in patients without risk factors for atherosclerotic disease.

Whether thyroid hyperfunction leads to increased coronary flow, the excessive acceleration of heart rate and myocardial high oxygen consumption can debunk a latent coronary failure giving an overt clinical expression. This especially in the 5th and 6th decades when atherosclerotic alterations of the vasculature becomes almost constant.

In our study one third of thyrotoxic patients preponderantly presenting arrhythmias or/and heart failure showed more or less discrete EKG modifications but without obvious clinical expression of coronary arterial failure. In 9 cases (18,3%) however painful ischemic events were prevalent striking apparently, either isolated or predominant between various other cardiovascular complaints. We also mentioned two patients presenting complete atrioventricular block, consequence of a "thyrotoxic myocarditis" and one case with sequelae of heart infarct. Clinical course of angina pectoris definitely aggravated by thyrotoxicosis though it was nevertheless significantly improves in 7 of 9 cases of surgical removal of hyperfunctioning lesion. Specific cardiovascular erethism including haemodynamic changes such as elevated cardiac output and increased blood volume described in thyrotoxicosis determined in severe cases to a rise in systolic blood pressure. However the overall prevalence in hypertension does not seem to be higher among the hyperthyroid patients than in euthyroid population. We recorded 7 cases of hyperthyroidism (14,2 %) with permanent or oscillating raised values of blood pressure. Normalisation of blood pressure values after thyroidectomy ascertained in 5 of our 7 patients, especially in young ones, emphasizing the more functional character of this trouble. In two of our cases we founded the association between hyperthyroidism and compensated mitral stenosis. Preceding the thyrotoxicosis which evolved concurrently for a period still exacerbating the valvular troubles. In both patients thyroid exeresis have benefited equally in terms of endocrine and cardiac troubles.

Overall in our series of cardiomyopathy in terms of pedantic indications, efficacious preparation and accurate technique, surgical treatment obtained good results both in thyroid lesions

remitted in without any serious postoperative morbidity in all situations and also in cardiac component clinically cured in 23 (46,9%) cases, ameliorated in 20 (40,8%) cases and stationary in the rest of 6 (12,2%) patients. (Table 2)

Discussions

The cardiovascular signs and symptoms are some of the most characteristic and common findings accompanying thyrotoxic syndromes. Hypertyroidism also has significant cardiovascular consequences even when the treated patient became euthyroid, this one being still prone to heart troubles. Thyroid hormone effects include reduction in systemic vascular resistance, increasing heart rate, left ventricular contractility and blood volume. (28,29)

Active form of thyroid hormone T3 via deiodination of tiroxine, have both genomic and nonge-nomic (extracellular) effects on cardiac myocyte. Genomic mechanism include T3 binding to specific nuclear receptorprotein (TRs) which resulted in increased transcription of T3-responsive specific cardiocirculatory genes. Nongenomic effects which occurs independent of nuclear T3 receptor binding influence primarily the transport of aminocids, sugars and calcium across the cell membrane. Both genomic and nongenomic actions of T3 can interface at the level of sarcoplasmic reticulum Ca²⁺-ATPase where gene expression is regulated by the T3 receptor complex and activity of the enzyme can be modulated nongenomically. (31,32)

Pathogenic diagnosis of so called "cor thyreotoxicum" is not always easy on account of cardiovascular syndrome which frequently overshadowed the thyroid subclinical picture or also issue of new appearing entities as amiodarone induced thyrotoxicosis (33,34,35)

Regarding management, pharmacologic therapy of cardiomyopathy obtain only transient or incomplete results therefore radical thyroeliminating procedures i.e. I 131 or surgery should have preference. Even if a single administration of a whole calculated dose of I 131 is the method of first choice in numerous centers worldwide, surgery is also preferred by many authors. (14,36,37,38,39,40)

In this retrospective series 49 surgical treated cases with different cardiovascular sufferings associated with current

Table 2. Postoperative results in thyrotoxicosis associated with cardiovascular sufferings

	Operated cases	Cured	Ameliorated	Stationary
Extrasystolic arrhythmia	4	3	1	-
Auricular fibrillation	14	9	3	2*
Auricular flutter	1	1	-	-
Postoperative fibrilloflutter	2	2	-	-
Cardiac failure	10	3	6	1
Ischemic coronaropathy	9	-	6	3
Arterial hypertension	7	5	2	-
Rheumatismal mitral stenosis	2	-	2	-
TOTAL	49	23/46,9%	20/40,8%	6/12,2%

*subsequent cardioversion

clinical forms of thyroid hyperfunction is presented. The first component was not always clearly delimited in its etiopathogenical origin even in patients when the clinical features diminished or even disappeared after endocrine exeresis. The surgical option depended on the severity of both thyrotoxicosis and cardiac troubles, the preoperative treatment was directed on a combination of target in the thyroid synthetic secretory and peripheral pathway to render the patient as close as possible to clinical and biochemical euthyroid before operation, with concurrent therapy to correct any cardiac anomaly of normal heart mechanism or function.

Variable combinations including iodine, thionamides, β -blockings agents, corticosteroids and even dexamethasone were used as initial medication to inhibit hormone synthesis and secretion as to reduce the conversion of T4 to T3 and the peripheral effects of thyroid hormones achieving endocrine equilibrium in the shortest interval.

Equally, in collaboration with the cardiologist, we have provide the appropriate antiarrhythmic, tonicardiac, coronarodilatatory and antihypertensive medication.

With a tenacious preparation in a relative short time (7-10 days) we obtained both the endocrine and cardiovascular equilibrium formulating an ensured surgical indication. General anesthesia with intubation and intermittent positive pressure ventilation was considered the safest approach for such procedures being preferred in most glandular exeresis excepting two cases of video-assisted lobectomy for TA in which we used superficial cervical plexus block.

Concerning surgical technique we endeavored to respect the principles of gentle dissection, meticulous hemostasis and anatomical exeresis consecrated in thyroid surgery. In our series we don't experienced any nerve injury or evidence of hypoparathyroidism.

However two cases with marked clinical syndrome and inveterate rhythm disturbances showed immediate after surgery prolonged sequences of atrial fibrillation, probably framed in an atypical thyrotoxic crisis (hyperpyrexia and agitation missing), remitted with difficulty after energetic β -adrenoceptor blockade and supportive therapy.

The good postoperative results obtained in our series were strengthened by appropriate complimentary medical treatment and continuous follow-up in multidisciplinary assistance including also endocrinologists and cardiologists.

In conclusion heart manifestations of hyperthyroidism realize a particular nosologic group with a controversial etiopathogenic mechanism, not always incriminated in glandular hyperfunction, but having a real gravity determined by the severity of either thyroid or cardiovascular disorders as their occurrence at ages above and especially their resistance against common effective therapy. Presence of these troubles significantly select the surgical indication, formulated with high discernment only after careful equilibration of both components, glandular and cardiac.

Conflict of interest

The authors declares that there is no conflict of interest regarding the publication of this article.

Contribution of authors

MRD conceived the study and performed surgery, MDD and GD diagnosed and monitored the patients, SD drafted the study.

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