Thyroid Hormone Levels in Patients with Aortic Dissection. Comparison with Controls and Correlation with the Percentage of the Aortic Media Composed of Myxoid Deposits

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Objective *- Deposits of myxoid material, similar to myxedema related to thyroid disease, are described in the medial layer of aortas with dissection. We analyzed the clinical or subclinical thyroid dysfunction of patients with this disease and analyzed whether a correlation exists between serum levels of thyroid-related hormones and the myxoid content of the aortic media.*

Methods *- We measured, with standard methods, serum levels of triiodothyronine (T3), thyroxine (T4), and thyroid stimulating hormone (TSH) in 28 patients who underwent aortic dissection and free T4 in 20 of them. The same hormones were quantified in 20 control patients matched by sex and age. Results were compared by using the Mann-Whitney test. We also measured the percentage of the aortic media occupied by myxoid material in the surgical specimens of 25 of the patients with aortic dissection and analyzed its correlation with hormone levels by using the Pearson test.*

Results *- In the 20 pairs in which the amount of hormones was compared, the mean values for T3, T4, free T4, and TSH were 1.22ng/mL, 9.89mcg/dL, 1.18ng/dL, and 5.45 microIU/mL in study patients and 1.15ng/mL, 8.57mcg/dL, 1.32ng/dL, and 2.15 microIU/mL in controls. Neither these differences nor the correlation between the percentage of myxoid content (mean=30%) and the values for T3, T4, free T4, and TSH (mean 1.22ng/mL, 9.44mcg/dL, 1.20ng/dL, and 5.08 microIU/mL, respectively; n= 25) were significant.*

Conclusion *- Our data suggest that serum levels of thyroid hormones have no relation with the myxoid content in the aortic media in cases of aortic dissection.*

Key-words: aorta, aneurysms, dissecting, thyroid hormones

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Aortic dissection (dissecting aneurysm) is characterized by the separation of the aortic wall into 2 sheets at the medial layer, along the longitudinal axis of the artery, thus forming a false channel for the blood flow [1] (fig. 1). It is a life-threatening but relatively rare disease, whose incidence has been evaluated in 5-29 cases/million persons/year [2,3]. Several conditions are associated with it: systemic arterial hypertension, the most common (70-90% of the cases); Marfan's syndrome; Hurler's syndrome; and traumatism, including surgical management of the aorta [1]. A small percentage of patients have no associated conditions. The pathogenesis of this disease remains unclear. Although most patients with aortic dissection have systemic arterial hypertension, they correspond only to a very small percentage of people with this last condition. Weakness of the wall is presumed to be present, but the actual factors underlying it have not been discovered [4]. Histological analyses targeting this objective describe 3 main findings in the media of aortas with dissection: fragmentation of elastic fibers, a decrease in the number of smooth muscle cells, and an increase in mucoid, basophilic material [5], a pattern frequently called "mediocystic necrosis" (fig. 2). In spite of being more prominent in such cases, these alterations are not specific to the dissection; they can also appear with aging, as secondary phenomena in many aortic diseases, and in patients with hypertension but not dissection [5].

The mucoid material, increased in aortic dissections, is one of the more important components of the medial layer. Proteoglycans, composed of a protein core and lateral chains of glycosaminoglycans, a family of long-chained sugars; or glycosaminoglycans such as hyaluronan (hyaluronic acid) by themselves are the molecules that give the tissues this histological characteristic [6], also called myxoid (myxos=mucus). This material is similar to pretibial or retroocular myxedema present in some patients with thyroid diseases.

In a necropsy series [7], more pathologic alterations were found in thyroids from patients with aortic dissection than from controls paired by sex, age, systemic arterial hypertension, and diabetes. The authors considered that part of the alterations (multiple nodular goiter, acinar atrophy and fi-

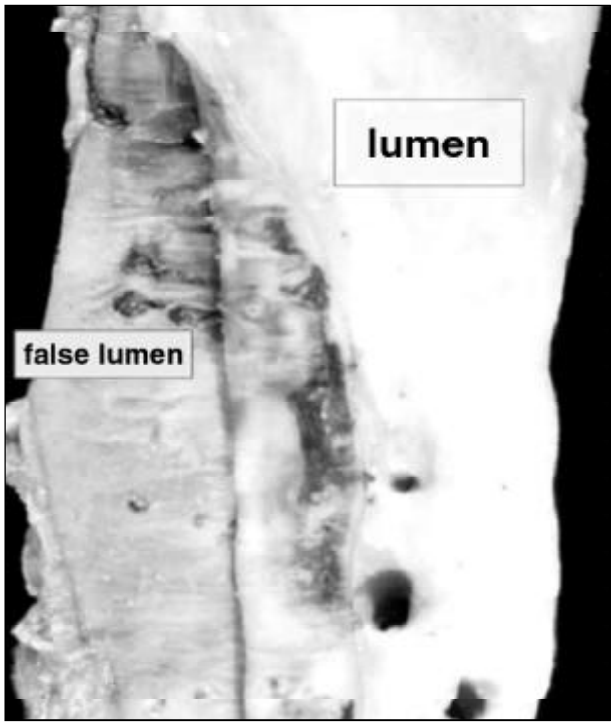

Fig. 1 - Macroscopical view of a segment of human aorta with the dissection, characterized by the separation of the wall into 2 sheets at the medial layer. A false lumen is created.

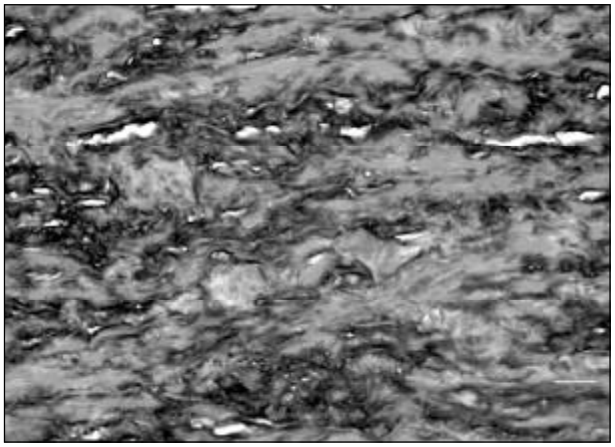

Fig. 2 - Histologic section of the medial layer of an aorta with dissection, stained with Alcian-blue to display proteoglycans, and counterstained with hematoxylin (pink). Objective magnification: 40x; bar (lower right corner)=20µm.

brosis, thyroiditis including Hashimoto's disease) could cause hypothyroidism, but this condition was documented with clinical and biochemical evaluations of thyroid function in only one of their cases.

Thus, aortic dissection could occur preferentially in persons with systemic arterial hypertension and thyroid disorders. The objective of the present study was to verify whether patients with aortic disease have an association with clinical or subclinical thyroid dysfunction, both by checking the relation between mucoid content in the aortic media and serum levels of thyroid hormones and by comparing these levels with those of control patients without aortic disease.

Methods

Twenty-eight patients (21 males) who had undergone surgical correction of aortic dissection in the ascending aorta (dissection type A according to the Stanford classification [8] or types I or II according to De Bakey's classification [9]) were included in the study. Only persons who had been operated on were selected in order to to make the group homogenous, because in most patients surgery is indicated as soon as possible after the diagnosis is established, considering the life-threatening nature of the disease. Age ranged from 37 to 76 years (mean 58, median 59). The main clinical data of these patients are presented in table I.

Patients who had undergone coronary artery revascularization with aortotomy were enrolled as controls. They were matched with the aortic dissection patients with regard to sex and age.

Triiodothyronine (T3), thyroxine (T4), free T4, and thyroid stimulating hormone (TSH) were quantified in the sera of the study patients and of 20 control patients by standard methods (radioimmunoassay, chemoluminescence, or IRMA). In 8 patients, free T4 was not measured.

Three-micrometer sections of the aortas of 25 patients, sampled during surgery, were stained with Alcian blue (a dye that stains in blue glycosaminoglycans, including those that take part in the composition of proteoglycans). To increase contrast, the sections were counterstained with hematoxylin (fig. 2). The slides were examined under a Leica microscope coupled to a Quantimet image analysis system, using a 40x objective. Blue areas were quantified by detection, and the total area of the aortic media was measured. The medial layer of each sample was scanned perpendicularly to the long axis of the aortic wall. The quantifications were performed in at least 20 screen fields. Additional fields were also measured after the 20th, until a total length of the media was completed. Mean percentage of area occupied by myxoid material was then calculated in each aorta.

SPSS for Windows 6.0 was used for the statistical study. The amount of thyroid hormone in case and control groups was compared using the Mann-Whitney rank sum test, and the presence of systemic arterial hypertension in these 2 groups was compared using Fisher's exact test. Due to the absence of control cases, only data of 20 patients (14 concerning free T4) were included in these analyses. Correlation between the percentage of mucoid content and hormone levels was verified by the Pearson test in 25 of the study patients, because the aorta was not sampled in the remaining 3 cases. Tests with $P \leq 5\%$ were considered significant.

Results

Sixteen of 20 patients with aortic dissection (80.0%) and 10 of 14 controls (71.4%; information not found about 6 of them) had systemic arterial hypertension. Therefore, the groups were not different concerning the proportion of hypertensive patients (P=0.69).

Two of the study patients and one control were known to have thyroid disease and had been treated pharmacologically; one of them had a low level of TSH.

Table I - Clinical features of patients with aortic dissection

Case number	Age	Sex	SAH	Time of evolution*	Dissected region	Duration of dissection	Observations
1	37	F	No	1 year	A+D	2 months	Annuloaortic ectasia
2	42	M	Yes	9 months	A	Chronic	
3	43	M	Yes	1 year	A+D	< 1 day	
4	43	M	Yes	8 months	A+D	3 days	
5	45	M	Yes	4 years	A	Chronic	Gout
6	46	M	Yes	5 months	A	10 days	Previous CABG; Hbs Ag+
7	47	M	Yes	5 months	A	~2 weeks	
8	51	F	Yes	1 year	A	Chronic	Previous aortic aneurysm; dyslipidemia
9	53	M	Yes	11/ 3years	A + (A+D)	Acute / Chronic	
10	55	M	Yes	4 years	A+D	2 days	Obesity
11	57	M	Yes	9 / 3 years	A + A	<1 day, Chronic	Redissection; previous myocardial infarction
12	58	F	Inc	10 months	A	Chronic	Known thyroid illness
13	59	M	Yes	6 months	A+D	< 1 day	Previous CABG
14	60	M	Yes	1 year	A+D	Chronic	Gastric adenocarcinoma
15	62	F	Yes	14 years	A	Chronic	Diabetes mellitus, obesity
16	63	F	Yes	4 months	A	Chronic	Uterine neoplasia
17	64	M	Yes	3.5 years	A	Chronic	Peptic ulcers
18	65	M	Yes	12 years	A+D (?)	1 day	
19	65	M	Inc	11 years	A+D	14 days	
20	66	F	Yes	12 months	A	Chronic	Known thyroid illness; previous CABG
21	66	M	Yes	6 months	A+D	< 1 day	
22	67	M	No	1 year	A	< 1 day	
23	67	M	Yes	14 months	A	Chronic	Annuloaortic ectasia
24	70	M	Yes	2 years	A+D	6 months	
25	71	F	Yes	10 months	A	< 1 day	Dyslipidemia
26	71	M	Yes	1 year	A (?)	< 1 day	Dyslipidemia; iatrogenic dissection
27	74	M	No	9 months	A (?)	< 1 day	Dyslipidemia; iatrogenic dissection
28	76	M	Yes	10 months	A	Chronic	

F - female; M - male; SAH - systemic arterial hypertension; Inc - inconclusive data concerning SAH; * - interval between surgery and serum sampling; A - ascending aorta; D - descending aorta; § - interval between start of symptoms and surgery (chronic - more than 2 weeks) HBs Ag+ - positive serology for hepatitis B virus; CABG - coronary artery bypass graft.

The amounts of T3, T4, free T4, and TSH in the serum are shown in Table 2. Besides the 3 patients mentioned above, hormonal alterations compatible with hyperthyroidism (a high level of free T4 and low TSH) were present in 2 study patients and 3 controls. High TSH, suggestive of hypothyroidism, either clinical (low free T4) or subclinical (normal free T4), was found in 2 patients in each group and in 1 aortic dissection patient in whom the free T4 level was not measured.

No significant difference was found between study patients and controls concerning hormone levels.

Table 3 and figure 3 present the percentage of area occupied by mucoid material in the first group. No correlation was found between the hormone levels and the percentage of area of myxoid material.

Discussion

Although controversial [10], some evidence exists that thyroid-disease associated deposits may not be restricted to pretibial or retroocular myxedema, but rather somehow are generalized [11]. Thus, since the decades following the description by Gsell and Erdhein in the 1920s of an increased amount of basophilic substance in the aortas with dissection, studies have tried to verify a possible relationship between thyroid dysfunction and this arterial disease. Kountz and Hempelmann [12] found a great percentage of cases of aortic dissection in patients undergoing thyroidectomy as a treatment for hypertension, but no association between the 2 pathologic conditions was found by Burchell [13]. More recently, a case was reported [14] in which an iatrogenic dissection followed coronary angioplasty in a patient with myxedema, but a series [15] analyzing 48 patients with subclinical or overt hypothyroidism suggested that the outcome after this procedure was not different from that in euthyroid patients. In 1994, Rosenmann and Yarom [7] reported an increased frequency of thyroid pathologic lesions in patients with aortic dissection, although without correlation with either clinical or biochemical evaluation of thyroid function.

On the other hand, glycosaminoglycans, composing or not proteoglycan chains, probably give the myxoid histological aspect to both thyroid disease-related and aortic dissection-related deposits, but the types of sugar chains involved may be different. Indications exist that either hyaluronan or decorin, a small sulfated proteoglycan, may be linked to thyroid-related deposits [16-19], whereas in a previous study we analyzed by immunohistochemistry the mucoid-increased areas in aortas with dissection, and neither decorin nor hyaluronan was marked [20]. Despite this discrepancy, the actual nature of each of these deposits is not fully elucidated, and it is not possible to rule out that a link between them might exist.

Evidence against the link between thyroid dysfunc-

Table II - Age, sex, presence of systemic arterial hypertension and hormone levels in 20 patients with aortic dissection and in controls

Case	Sex	Age		SAH		T3 (ng/mL)		T4 (mcg/dL)		Free T4 (ng/dL)		TSH (microIU/mL)	
		AD	C	AD	C	AD	C	AD	C	AD	C	AD	C
5	M	45	45	Y	Y	1.5	1.9	11.0	9.8	1.6	1	2.3	1.4
7	M	47	49	Y	Y	0.9	1.1	6.5	11.1	0.87	1.4	2.8	1
9	M	53	54	Y	Y	1.4	0.8	12.1	9.0	0.9	1.4	1.4	1.9
10	M	55	55	Y	Y	1.7	0.9	12.1	9.9	1.9	1.9	0.5	0.9
11	M	57	59	Y	Y	1.9	1.1	11.3	12.2	1.1	2.6	1.2	0.6
12	F	58*	57	I	Y	1.1	1.4	7.4	8.9	-	1	2.2	11.1
13	M	59	61	Y	I	0.9	0.8	8.1	8.6	0.6	1.1	6.3	0.5
14	M	60	63	Y	Y	0.7	0.9	9.3	9.4	1.3	1.4	2.1	2.1
15	F	62	62*	Y	I	1.1	2.1	19.7	9.7	1.9	1.1	0.4	5.7
16	F	63	65	Y	Y	1.66	1.1	8.9	6.1	1.2	1.1	1.4	3.7
17	M	64	64	Y	I	1.6	0.9	9.3	6.9	1.2	1.2	0.8	2.6
18	M	65	65	Y	N	1.6	1	18.5	8	-	1.3	1	0.9
19	M	65	65	I	I	1.1	0.9	7.6	7	1.2	1.5	2.8	1.3
21	M	66	66	Y	N	1.8	1.4	12.4	8	1.3	1	1.3	1
22	M	67	68	N	Y	1.2	1.3	10.2	8	-	1.2	< 0.1	0.7
23	M	67	68	Y	I	0.9	1.6	9.1	9.1	-	1.4	3.1	0.5
25	F	71	71	Y	I	0.6	1.1	6.7	9.8	1.2	1.3	3	0.2
26	M	71	70	Y	Y	1.1	0.9	7.7	7.5	-	1.2	2	1.8
27	M	74	72	N	N	0.7	0.7	<2.5	6.5	0.27	1	72.8	4.7
28	M	76	73	Y	N	1	1.1	7.5	5.9	-	1.2	1.5	0.6
Mean		62.25	62.60			1.22	1.15	9.89	8.57	1.18	1.32	5.45	2.15
Median		63.5	64.5			1.1	1.1	9.2	8.75	1.2	1.2	1.75	1.15
Normal						0.8 – 2.0		4.5 – 12.5		0.8 – 1.9		0.3 – 4.5	
P				0.69		0.48		0.30		0.51		0.35	

SAH - systemic arterial hypertension; AD - patients with aortic dissection: C - control patients; T3 - triiodothyronine; T4 - tyrosine; TSH - thyroid stimulating hormone; Y - yes; N - no; I - inconclusive concerning SAH; - - free T4 not measured; * - patients with known clinical thyroid disturbances. *Note*: for statistics calculations, T4 in patient 29 and TSH in patient 23 were taken as 2.4 and 0.09, respectively.

Table III - Thyroid hormone levels and percentage of aortic medial layer occupied by mucoid substance

Case	T3 (ng/ml)	T4 (mcg/dl)	Free T4 (ng/dl)	TSH (microUi/ml)	% mucoid
1	1.5	11.4	1.5	3.0	37
2	1.3	9.2	1.4	0.5	28
3	0.8	13.7	-	4.3	35
4	1.5	10.0	1.3	1.9	25
5	1.5	11.0	1.6	2.3	15
6	0.9	7.3	1.4	2.4	32
7	0.9	6.5	0.9	2.8	26
8	1.1	6.7	-	3.5	28
9	1.4	12.1	0.9	1.4	40
11	1.9	11.3	1.1	1.8	29
12	1.1	7.4	-	2.2	37
13	0.9	8.1	0.6	6.3	22
14	0.7	9.3	1.3	2.1	23
16	1.7	8.9	1.2	1.4	23
18	1.6	18.5	-	1.0	29
19	1.1	7.6	1.2	2.8	24
20	1.9	10.8	1.6	0.2	31
21	1.8	12.4	1.3	1.3	25
22	1.2	10.2	-	< 0.1§	28
23	0.9	9.1	-	3.1	22
24	1.0	9.1	1.6	3.9	31
25	0.6	6.7	1.2	3	31
26	1.1	7.7	-	2.0	57
27	0.7	<2.5*	0.27	72.8	40
28	1.0	7.5	-	1.5	33
R	-0.15	-0.14	-0.27	0.23	
P	0.47	0.49	0.30	0.27	

T3 - triiodotyronine; T4 - tirosine; TSH - thyroid stimulating hormone; - - free T4 not measured; * - for statistical purposes, value was computed as 2.4; § - for statistical purposes, value was computed as 0.09; r - correlation coefficients between % mucoid and each thyroid hormone levels.

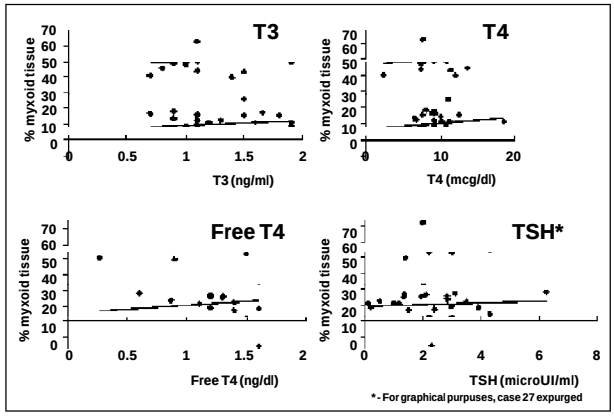

Fig. 3 - Relation between thyroid hormone levels and percent area of myxoid tissue in the aortic medial layer.

tion and aortic dissections indicates that the first disease is more common in women, while most cases of the arterial illness occur in men (3:1 male/female ratio [21], approximately the same present in our study patients).

Thus, considering not only the presence of myxoid material in both conditions, but also the controversy concerning a possible association between them, we carried out the present study aiming to determine whether clinically evident or subclinical thyroid dysfunction was present in patients with aortic dissection. Only patients in the late, stable postoperative period of aortic dissection were selected to avoid biasing the findings with alterations that could be re-

lated to critical status. In accordance with accepted criteria[22], thyroid function was evaluated by the serum level of T3, T4, free T4, and mostly TSH.

We found no differences between patients with aortic dissection and controls, which were selected from patients who were age and sex-matched to the study patients and who had also undergone aortotomy (during coronary artery by-pass graft surgery). Additionally, no relation was present between hormone levels and the morphometric quantification of myxoid tissue in the aortic medial layer in the cases of dissection. Therefore, our data indicate that serum levels of thyroid hormones have no relation to arterial disease.

As a study limitations, thyroid disturbances could be secondary to ischemia caused by the aortic dissections; nevertheless, ischemia is not commonly taken into account as a significant factor involved in thyroid disease. On the other hand, some patients were in a very late postsurgical period (up to many years). Modifications in thyroid function could have occurred after the dissection. These possibilities would have greater implications if the results had shown either differences between the 2 groups or that the myxoid content was related to the hormone levels.

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