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Amiodarone-induced thyroid dysfunction in an iodine--replete area: epidemiological and clinical data

Zaburzenia czynności tarczy indukowane amiodaronem w regionie bogatym w jod: dane epidemiologiczne i kliniczne

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Abstract

Introduction: The present study aims to evaluate the incidence, types, timing and risk factors in amiodarone (AMD)-induced thyroid dysfunction.

Material and methods: The study comprised 229 patients from an iodine-replete area (115 women, 114 men, mean age 63.8 ± 9.2 years), chronically treated with AMD. The cases were clinically investigated prior to, and during treatment, by thyroid 2D and color Doppler flow sonography, thyroid function tests (TSH, FT_3, FT_4), and antithyroid antibodies.

Results: Of 88 patients (38.4%) who developed thyroid dysfunction, 47 (20.5%) presented AMD-induced thyrotoxicosis (AIT) and 41 (17.9%) AMD-induced hypothyroidism (AIH). There is an evident prevalence of subclinical AIH (29 cases), compared to subclinical AIT (three cases). Regarding clinical forms, these prevailed in AIT (44 patients) ($p < 0.001$, Fisher's exact test). Thyrotoxic patients were classified in pathogenic types as follows: 11 cases as type 1, 15 cases as type 2, and 21 cases as mixed form. The most important risk factor for the development of thyroid dysfunction was represented by the underlying thyroid pathology. The patients with previous thyroid abnormalities (diffuse or nodular goitre and/or positive antithyroid antibodies) developed earlier thyroid dysfunction compared to those with an apparently normal thyroid gland. The thyroid dysfunction occurrence was heterogeneous (4–84 months). Thyrotoxicosis involved especially young ages, while AIH affected later years.The daily dose, the duration of the treatment and the cumulative dose of AMD do not represent risk factors in thyroid dysfunction development. The determination of serum AMD and desethylamiodarone concentrations does not offer benefits in the diagnosis and treatment of thyroid dysfunction.

Conclusions: In the present study, the incidence of AIH was similar to that reported in iodine-replete areas. The incidence of AIT was higher that previously reported, a fact underlining the importance of the proper screening and monitoring of patients. Cases with previous thyroid morphologic and/or immunologic abnormalities require frequent monitoring. **(Pol J Endocrinol 2012; 63 (1): 2–9)**

Keywords: *amiodarone, thyroid dysfunction, thyrotoxicosis, hypothyroidism*

Streszczenie

Wstęp: Badanie przeprowadzono w celu oceny zapadalności na zaburzenia czynności tarczycy indukowane amiodaronem (AMD).

Materiał i metody: Badanie obejmowało 229 chorych zamieszkujących region bogaty w jod (115 kobiet, 114 mężczyzn; średnia wieku 63,8 ± 9,2 roku), długoterminowo leczonych AMD. Przed i w trakcie terapii u uczestników przeprowadzono ocenę kliniczną, badanie USG 2D i techniką kolorowego doplera, testy czynności tarczycy (TSH, FT_3, FT_4) oraz oznaczono przeciwciała przeciwtarczycowe.

Wyniki: Spośród 88 chorych (38,4%), u których rozwinęły się zaburzenia czynności tarczycy, u 47 (20,5%) stwierdzono indukowaną AMD tyreotoksykozę (AIT), a u 41 (17,9%) — indukowaną AMD niedoczynność tarczycy (AIH).

W badanej grupie odnotowano zdecydowanie więcej przypadków subklinicznej AIH (29 przypadków) niż subklinicznej AIT (3 przypadków). Porównanie częstości jawnych klinicznie postaci zaburzeń czynności tarczycy wykazało przewagę AIT (44 chorych) ($p < 0,001$, dokładny test Fishera).

Osoby z tyreotoksykozą sklasyfikowano w zależności od typu patogenetycznego: 11 przypadków jako typ 1, 15 przypadków jako typ 2 i 21 przypadków jako postać mieszaną.

Najważniejszym czynnikiem ryzyka rozwoju badanych zaburzeń były choroby tarczycy. U chorych, u których wcześniej stwierdzono nieprawidłowości w badaniach tarczycy (wole rozlane lub guzkowe i/lub obecność przeciwciał przeciwtarczycowych), zaburzenia czynności gruczołu rozwijały się wcześniej niż u osób, u których wyniki badań były prawidłowe.

Zaburzenia czynności tarczycy pojawiały się sie w różnym czasie (w ciągu 4–84 miesięcy). Tyreotoksykoza występowała głównie u osób młodych, natomiast AIH rozwijała sie w późniejszym wieku.

Dawka dobowa, czas trwania terapii i skumulowana dawka AMD nie stanowiły czynników ryzyka rozwoju zaburzeń czynności tarczycy. Określenie stężeń AMD i desetylamiodaronu w surowicy nie było pomocne w rozpoznaniu i leczeniu zaburzeń czynności tarczycy.

Wnioski: Zapadalność na AIH w badanej grupie była podobna, jak w innych regionach bogatych w jod. Liczba nowych przypadków AIT była większa niż opisywana wcześniej, co podkreśla znaczenie badań przesiewowych i monitorowania pacjentów. Zwłaszcza osoby z nieprawidłowościami w zakresie budowy tarczycy i zaburzeniami immunologicznymi wymagają częstych badań kontrolnych. **(Endokrynol Pol 2012; 63 (1): 2–9)**

Słowa kluczowe: *amiodaron, zaburzenia czynności tarczycy, tyreotoksykoza, niedoczynność tarczycy*

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Introduction

The present study regards a topic of general interest, because amiodarone (AMD)-induced thyroid dysfunction may be associated with significant morbidity and mortality.

AMD is a very widely used antiarrhythmic drug. Its structure resembles that of thyroid hormones, and hence some of its antiarrhythmic and toxic effects might be due to interactions with thyroid hormones nuclear receptors [1].

AMD and its major metabolite, desethylamiodarone (DEA) have a long half-life of 16 to 180 days [2].

Prolonged administration of AMD can be associated with numerous side effects, one of the commonest being thyroid dysfunction [3].

AMD affects the thyroid gland by its high iodine content (37% of its molecular weight) and/or direct toxic effect on thyroid cells [4].

In the evaluation of a patient chronically treated with AMD, its complex effects on the thyroid must be considered [5]. Hence, 30–40% of the subjects treated over three months might present altered laboratory tests, such as high-normal free T_4 (as much as 40% above basal values) or low-normal free T_3 associated with normal TSH [3].

Although most patients remain euthyroid during AMD treatment, 2–24% can develop thyroid dysfunction, ranging from asymptomatic altered laboratory findings to overt disease [6].

Most authors have reported a higher incidence of AMD-induced hypothyroidism (AIH) in iodine-sufficient areas, with the incidence ranging from 6% in iodine-deficient regions to 13% in iodine-repleate zones [7, 8]. Amiodarone-induced thyrotoxicosis (AIT) is considered to prevail in iodine-deficient areas, where it exceeds 13% [9, 10]. These discrepancies of AIH and AIT incidences may be due to: different diagnostic criteria, various iodine intake, different monitoring schedules, or geographical differences [11].

Generally, AIH develops earlier than AIT, usually during the first 18 months of treatment [7, 12]. It can occur in patients with previous thyroid abnormalities, but also in those with apparently normal thyroids [13, 14].

The main risk factor is represented by chronic autoimmune thyroiditis; 40% of patients who develop AIH present positive antithyroid antibodies. This suggests that iodine excess from AMD could unmask a pre-existing subclinical thyroid disease [15–17]. Other possible mechanisms have been described as being involved in AIH development [18, 19].

AIT predominates in men, probably due to a higher prevalence of cardiac diseases [20]. AIT is unpredictable, occurring any time during AMD treatment and even after drug interruption, because of its long half-life [2, 21].

The risk factors involved in AIT occurrence remain controversial. A pre-existing thyroid disease (nodular goitre, thyroid with functional autonomy) and a previous iodine deficiency are the main predisposing factors [22, 23]. Certain genes could also increase susceptibility [24].

AIT is classified arbitrarily into two major forms, based on clinical and laboratory parameters [25]. The differentiation into pathogenic forms is important for the therapeutic approach, although some studies suggest that the subtype does not influence the outcome [26–28]. Type 1 is an iodine-induced hyperthyroidism, developed in patients with previous thyroid abnormalities (latent Graves' disease, nodular goitre). Type 2 represents a destructive form of thyroiditis, and occurs in subjects with previous apparently normal thyroid glands [2, 5].

Screening and monitoring of thyroid functionality in AMD-treated patients remains a subject for discussion, since a universal schedule is lacking. So far, several different guidelines have been proposed, one of the most widely accepted having been developed by the North American Society of Pacing and Electrophysiology in 2000 [29].

Before introducing AMD treatment, the basal thyroid screening should include: clinical exam, thyroid ultrasound, and determination of serum TSH, FT_3, FT_4 and antithyroid antibodies.

Some authors recommend endocrinological reevaluation every six months without monitoring the initial three months of treatment with AMD [30]. Others consider necessary a first evaluation at three months after starting therapy, and regular monitoring every six months, or if a clinical suspicion of thyroid dysfunction arises [6].

The aims of the present study were to evaluate the prevalence, types, timing and risk factors in AMD-induced thyroid dysfunction, in an iodine-sufficient region.

Material and methods

Our study included 229 AMD chronically treated patients (115 women, 114 men, mean age 63.8 ± 9.2 years). The subjects, from an iodine-replete area, were investigated in the Clinic of Endocrinology, Timisoara, Romania, in the period October 2004 to September 2010.

The study inclusion criteria were age over 18 years and AMD treatment over three months. Subjects with thyroid morphology abnormalities (diffuse or nodular goitre) or positive serum antithyroid antibodies, associ-

ated with euthyroidism before AMD treatment, were included.

Patients with severe heart failure, incessant ventricular tachyarrhythmia not controlled by medical therapy, uncorrected severe valvular abnormalities, complex congenital heart disease or severe systemic illness were excluded. Those diagnosed with thyroid dysfunction prior to AMD therapy were also excluded.

Amiodarone-induced thyrotoxicosis (AIT) was defined as suppressed TSH (< 0.1 mU/L). Subclinical form presented normal serum T_3 concentrations (total and free) and normal or high-normal total and free T_4, without any clinical signs. Overt thyrotoxicosis showed elevated serum thyroid hormones. AIT was classified in two major forms. The diagnostic criteria for type 1 were as follows: diffuse or nodular goitre, increased thyroid vascularity in colour flow Doppler sonography, and positive antithyroid antibodies. AIT type 2 presented a normal thyroid volume or small goitre, no thyroid vascularity, and no positive antithyroid antibodies. Cases with features common to both types were considered to be mixed forms [2].

Overt amiodarone-induced hypothyroidism (AIH) was ascertained by high values of serum TSH and low thyroxin values, while the subclinical form included persistent slightly elevated TSH (4.5–20 mU/L) and normal or high-normal serum T_4, with no clinical signs [30, 31].

The study was approved by the local ethics committee. All patients provided oral informed consent.

Thyroid gland volume, morphology and vascularisation were assessed using B-mode and colour Doppler ultrasonography.

Serum TSH (third generation TSH, Architect i2000, Abbott Diagnostics), free T_4, free T_3 (CMIA, Architect i2000, Abbott Diagnostics), anti TPO antibodies (CMIA, Abbott Ax SYM System), antithyroglobulin antibodies (MEIA, Abbott Ax SYM System) and anti TSH receptor antibodies (TRAb) (Brahms Diagnostics, Berlin) were determined by commercial kits. Normal values were as follows: TSH 0.46–4.67 mU/L, FT_3 1.71–3.71 pg/ml, FT_4 0.71–1.85 ng/dL, TPO Ab < 12 U/L, Tg Ab < 35 U/L, and TRAb < 1U/L.

Serum concentrations of AMD and DEA were determined using high-performance liquid chromatography (HPLC) (in Heidelberg, Germany). The given therapeutic serum concentrations were 700–2,500 μg/L for AMD and 500–3,000 μg/L for DEA.

Statistical analysis

The data were nalysed using SPSS version 14 for Windows (SPSS Inc, Chicago, IL, USA). Normal distribution of continuous variables was assessed by Kolmogorov–Smirnov test or by histograms. Normal distributed continuous variables were expressed as mean ± SD, those without normal distribution as median values. Student's *t*-test was applied to compare continuous values with Gaussian distribution, while Mann–Whitney U-test was used for not normal distributed values. A p value below 0.05 was considered statistically significant. One-way ANOVA test was used to compare several mean values. To compare parametric data, Fisher's exact test was applied. Pearson or Spearman correlation tests were used as appropriate. To estimate the cumulative incidence of a binary event, a Kaplan–Meier survival curve was applied (95% confidence interval).

Results

Demographic data

Using the established diagnostic criteria during AMD treatment, the patients were divided into three groups: a euthyroid group (n = 141, 61.5%), a hypothyroid group (n = 41, 17.9%), and a thyrotoxic group (n = 47, 20.6%).

Most of the patients received AMD therapy for supraventricular arrhythmias (n = 192, 83.8%), and only 37 for ventricular arrhythmias. The underlying cardiac diseases were as follows: coronary heart disease (36.4%), hypertensive cardiomyopathy (18.4%), mixed cardiomyopathy (25.3%), valvular disease (16.5%), Wolff–Parkinson–White syndrome (three cases), atrial septal defect (one case) and hypertrophic obstructive cardiomyopathy (three cases).

The screening of thyroid function before introducing AMD treatment (at least TSH determination) was performed in 139 cases (60.6%) (Table I). The non-screened patients were evaluated during AMD treatment as soon as they entered the study. The euthyroid status during AMD therapy was confirmed in all patients who subsequently developed thyroid dysfunction.

After the initial evaluation, the hormonal investigations were repeated after three months. The new values were considered new reference values. Thereafter, the

Table I. *Baseline thyroid screening in studied cases*
Tabela I. *Wyniki wyjściowych badań tarczycy u osób badanych*

Parameter	Baseline screened cases
Complete thyroid evaluation	58 (25.3%)
Thyroid examination	
Thyroid ultrasonography	
TSH, FT_4, FT_3	
Antithyroid antibodies	
Clinical examination + TSH	81 (35.3%)
Not evaluated	90 (39.4%)

Table II. *Demographic, clinical and biochemical data in study groups (quantitative data expressed as mean ± SD)*

Tabela II. *Demograficzna, kliniczna i biochemiczna charakterystyka badanych grup (dane ilościowe przedstawiono jako wartości średnie ± SD)*

Parameter	Euthyroid group	AIH group	AIT group	p
Number of patients	141	41	47	
Gender (women/men)	74/67	24/17	17/30	0.076‡
Age (years)	64.8 ± 9.4	66.0 ± 7.4	57.5 ± 8.2	< 0.0001†
Duration of AMD therapy (months)	26.0 ± 24	23.7 ± 17.5	26.3 ± 16.4	0.82*
Median	18	17	24.5	
Cumulative dose of AMD [g]	152.4 ± 143.7	141.4 ± 98.2	154.2 ± 96.7	0.87†
Serum AMD concentration [μg/L]	666.5 ± 358.3	755.7 ± 472.2	558.8 ± 362.2	0.33†
Serum DEA concentration [μg/L]	663.4 ± 325.1	687.8 ± 303.7	525.5 ± 342.1	0.26†
Goitre at diagnosis (n)				
Diffuse	17	15	27	< 0.0001‡
Nodular	8	0	3	
Thyroid volume [ml]	19.2 ± 7.1	17.2 ± 7.2	24.0 ± 8.3	0.001†
Positive antithyroid antibodies (n, %)	22 (15.6%)	11 (26.8%)	11 (23.4%)	0.19‡

†One-way Anova test; ‡ χ^2 test; *non-parametric Mann–Whitney U-test

patients were evaluated every six months by TSH determination. The patients were evaluated immediately in case of arrhythmia during AMD therapy or if a thyroid dysfunction was suspected.

Women predominated in the hypothyroid group compared to the thyrotoxic group (p = 0.053, Fisher's exact test). The AIT group was significantly younger compared to the euthyroid and the hypothyroid group (57.5 ± 8.2 years, vs. 64.8 ± 9.4 years and respectively 66.0 ± 7.4 years, p < 0.001, *t* test). No statistically significant differences were noticed among study groups regarding mean duration of AMD treatment, mean daily dose, cumulative dose of AMD, or serum concentrations of AMD and DEA (measured in 113 patients) (Table II).

Thyroid dysfunction group parameters

The overt form prevailed in the AIT group (44/47) but not in the AIH group (12/41) (p < 0.001, Fisher's exact test).

Within the entire study group, 68 patients presented goitres: 11 nodular goitres and 57 diffuse goitres, with a similar percentage between women (n = 35) and men (n = 33).

The prevalence of goitre was significantly higher in the thyroid dysfunction group (n = 43, 48.8%), compared to the euthyroid group (n = 25, 17.7%, p < 0.0001, Fisher's exact test).

Thyrotoxic patients presented higher thyroid volumes (median volume 23 ml, limits 11–45 ml) compared to hypothyroid (median 16.7 ml, limits 7–40 ml) and euthyroid cases (median 15.8 ml, limits 9–38 ml) (p = 0.001, Anova test) (Table I).

In the AIT group, the mean age, the duration of AMD treatment until thyrotoxicosis developed, and the cumulative dose were similar among the pathogenic subgroups. Type 2 and mixed AIT patients were younger compared to type 1 (56.3 ± 8.07 years, respectively 55.3 ± 10.2 vs. 62.0 ± 3.9 years, p = 0.052 and respectively p = 0.06) (Table III).

One AIT diagnosis criterion was thyroid abnormalities. Thus, ten patients classified as type 1 AIT showed diffuse (seven cases) or nodular goitre. Seven patients were diagnosed as type 2, and 13 mixed forms presented diffuse goitre.

The prevalence of positive antithyroid antibodies was higher in the thyroid dysfunction group (22 cases, 25%) compared to the euthyroid group (22 cases, 15.6%, p = 0.08 Fisher's exact test).

Of the eight type 1 thyrotoxic patients with diffuse goitre, five presented positive titres of TRAb, unlike the other subgroups, where none of the patients had positive TRAb values.

A percentage of 14.7 of thyroid dysfunction cases presented previous thyroid pathology, as compared to 9.2% of euthyroid subjects. In the type 1 AIT group, six patients presented thyroid abnormalities: three nodular goitres and three diffuse goitres. In the mixed form group, three patients presented formerly known diffuse goitre, unlike type 2, with two cases of known thyroid abnormalities.

Table III. *AIT group parameters (values expressed as mean ± SD)*
Tabela III. *Badane parametry w grupie AIT (dane przedstawiono jako wartości średnie ± SD)*

Parameter	Type 1 (11 cases)	Type 2 (15 cases)	Mixed form (21 cases)	p
Age (years)	62.0 ± 3.9	56.3 ± 8.07	55.3 ±10.2	0.13†
Duration of AMD treatment (months)	26.9 ± 19.8	31.07 ± 17.7	21.3 ± 11.4	0.43‡
Cumulative dose of AMD [g]	160.8 ± 115.5	170.8 ± 110.8	133.0 ± 63.8	0.84‡
Thyroid volume [ml]	30.0 ± 8.2	18.6 ± 5.5	24.8 ± 7.9	0.005†
Goitre at diagnosis (n)	10	7	13	0.064*
Previous thyroid abnormalities (n)	6	2	3	0.02*
Positive antithyroid antibodies (n)	7	0	4	0.0006*
TSH [mU/L]	0.007 ± 0.006	0.008 ± 0.009	0.011 ± 0.01	0.71†
FT_4 [ng/dl]	4.65 ± 1.68	4.25 ± 1.59	4.41 ± 1.74	0.85†
FT_3 [pg/ml]	6.62 ± 1.85	6.2 ± 2.86	9.26 ± 6.11	0.18†

†One-way Anova test; ‡Kruskal–Wallis test; *χ^2 test

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Clinical data and arrhythmias

Most of the thyrotoxic patients, regardless of the pathogenic subtype, presented with major clinical symptoms: palpitations, mild weight loss, marked fatigue, tremor and dyspnoea. The clinical picture of the overt hypothyroid patients was unremarkable, with complaints mostly only consisting of asthenia and somnolence. Subclinical dysfunction cases were diagnosed by routine laboratory tests.

Three quarters of the thyrotoxic patients presented arrhythmias (new-onset or recurrent): 24 cases of atrial fibrillation, six of atrial flutter, and five cases with ventricular extrasystolia. The mean age of AIT patients with arrhythmias was similar to that of AIT subjects without arrhythmias (58.3 ± 7.0 years, vs. 54.3 ± 11.3 years, p = 0.16, *t* test).

No statistically significant differences were noticed regarding duration, cumulative dose or serum AMD and DEA concentration between the arrhythmic group and the sinus rhythm group. Thyrotoxic arrhythmic patients presented significantly lower values of TSH (mean 0.004 ± 0.005 mU/L, median 0.001 mU/L) compared to the non-arrhythmic group (mean 0.011 ± 0.008 mU/L, median 0.01 mU/L, p = 0.02, t test), associated with comparable serum FT_3 and FT_4 values.

Euthyroid and hypothyroid patients developed different arrhythmias, but at a smaller rate than AIT cases (22, respectively 7 cases) ($p < 0.0001$, χ^2 test).

Risk factors for thyroid dysfunction

As 38.4% of the patients developed thyroid dysfunction, the present study tried to establish the risk factors for developing a future thyroid disease.

The pattern of thyroid dysfunction development was heterogeneous (4–84 months).

The duration of AMD treatment until thyrotoxicosis developed was 26.3 ± 16.4 months (median 24.5 months). The rate of diagnosis was as follows: 25% at 13 months, 50% at 24 months, and 75% at 35 months. Hypothyroidism developed after 23.7 ± 17.5 months (median 17 months), the rate being similar to that of AIT (p = 0.749, Log rank Mantel-Cox test) (Figure 1). The rate of diagnosis was similar among pathogenic types of AIT.

The thyroid dysfunction group included 47 men and 41 women. Women developed thyroid dysfunction slightly earlier (mean 22.8 ± 17.4 months, median 16 months), compared to men (mean 26.8 ± 16.6 months, median 24 months), but the rate of diagnosis was similar (p = 0.301, Log Rank Mantel-Cox test).

The patients with previous thyroid abnormalities (diffuse or nodular goitre, positive antithyroid antibodies) developed thyroid dysfunction earlier (mean 18.2 ± 13.1 months, 95% confidence interval 12.7–23.8 months, median 14.5 months) compared to those without pre-existing thyroid abnormalities (26.2 ± 17.2 months, 95% confidence interval 22.0–30.5 months, median 24 months, p = 0.04, *t*-test).

The Log Rank Mantel-Cox test (p = 0.003) proved that the rate of diagnosis differed significantly in the group with thyroid abnormalities (25% at 11 months, 50% at 24 months, 75% at 36 months), compared to the group without pre-existing alterations (25% at 24 months, 50% at 42 months, 75% at 72 months).

The patients with positive antithyroid antibodies presented similar diagnosis rate of thyroid dysfunction as those with negative antibodies. However, those with

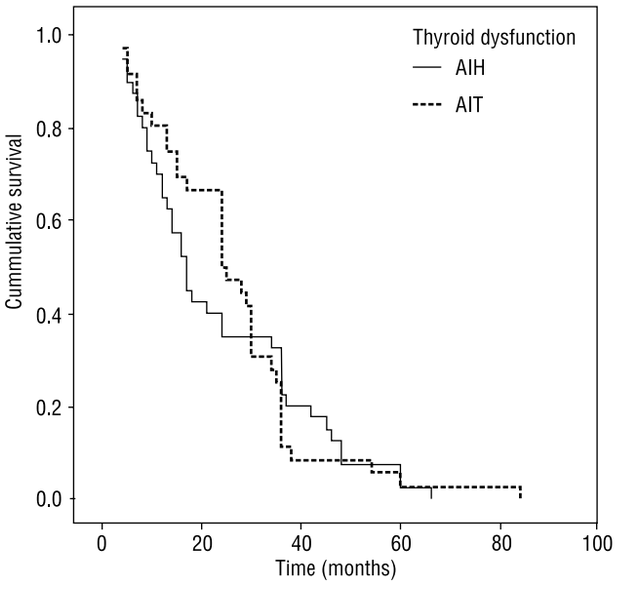

Figure 1. *Kaplan–Meier survival curve, representing the cumulative risk of thyroid dysfunction development and the period of time until diagnosis*

Rycina 1. *Krzywe przeżycia Kaplana-Meiera przedstawiające skumulowane ryzyko zaburzeń czynności tarczycy i czas do dokonania rozpoznania*

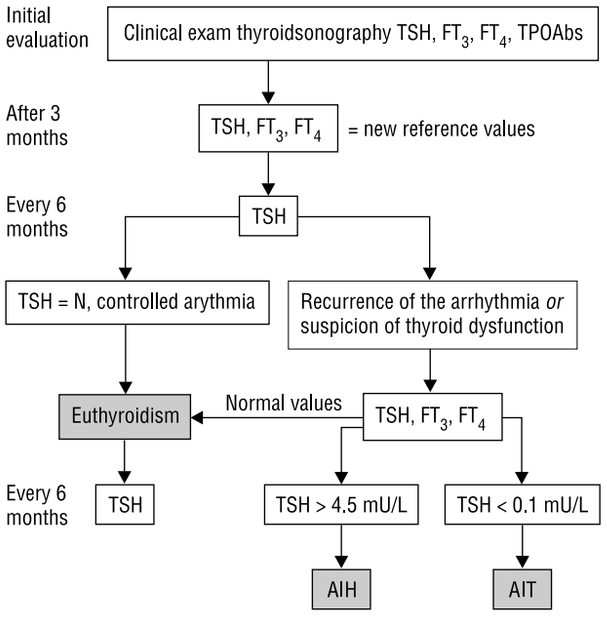

Figure 2. *Algorithm for following AMD-treated cases*

Rycina 2. *Algorytm obserwacji chorych leczonych AMD*

very high titres of antibodies developed the dysfunction earlier than those with low or negative titres, even though no statistically significant differences were noticed (p = 0.50, Log Rank Mantel-Cox test).

The age of the patients, the daily dose of AMD, the cumulative dose, the serum AMD and DEA concentrations, did not influence significantly the rate of thyroid dysfunction development.

Discussion

The incidence of thyroid dysfunction induced by AMD reported in the present study is similar to that in the literature, with a slightly higher percentage of the AIT, as previously reported [7, 11].

The incidence and severity of newly diagnosed thyroid dysfunctions are influenced by the screening and monitoring of patients.

A complete thyroid evaluation should be performed prior to AMD treatment to identify the subjects with risk factors for a possible future dysfunction. Additionally, in patients with nodular goitre, thyroid scintigraphy should be performed, even if TSH is normal.

Where morphological (diffuse or nodular goitre) or immunological (positive serum antithyroid antibody) abnormalities are detected, monitoring should be individualised, these cases presenting an increased risk for future thyroid dysfunction.

The prevalence of positive antithyroid antibodies was slightly higher in the AIH group (26.8%) compared to the euthyroid (15.6%) and the AIT groups (23.4%). In some patients, the titres appear to influence the occurrence of AIH, subjects with high titres developing the dysfunction earlier.

Patients with a serum TSH value at the upper limit of normal and/or positive antithyroid antibodies present an increased risk for the development of hypothyroidism [32].

Our screening rate was suboptimal (39.4% of the cases had not been evaluated before AMD treatment). The reported screening rate varies from 37% to 65.8% [33] and the rate of proper monitoring is also very heterogeneous, ranging from 2.9% [30] to 72.7% [21]. In order to increase patients' compliance with the monitoring process, it is necessary to develop an interdisciplinary algorithm. Figure 2 represents our proposed algorithm for screening and monitoring AMD-treated patients.

The rates of diagnosis of AIH and AIT were similar in our study. Some authors have reported a specific pattern: while AIT can develop at any time during AMD therapy, AIH occurs usually in the first months of treatment [8]. Other studies have reported a random pattern of occurrence, but with increasing incidence of AIT over time [7]. In the present study, the pattern of development of thyroid dysfunction was very heterogeneous (4–84 months).

The higher prevalence of subclinical AIH over the clinical form in our study group could be due to low progress of the subclinical form into the overt one.

The increasing incidence of AIT in iodine-replete areas suggests other possible pathogenic mechanisms, independent of iodine intake: thyroid autoregulation alteration induced by iodine, direct cytotoxic effects of AMD on thyroid follicles, specific genes, or increased susceptibility of some subjects to develop thyrotoxicosis [10, 24, 34].

A retrospective study by Bogazzi which included 215 patients with AIT (over 27 years) revealed a change in the prevalence of pathogenic types of thyrotoxicosis. The incidence of type 2 increased, while type 1 remained constant. The increasing incidence of type 2 could be explained by more careful screening and monitoring in recent years, the administration of AMD for longer periods, and the avoidance of AMD treatment in patients with thyroid abnormalities [35, 36].

The increasingly sensitive methods for determining TSH have led to an improved diagnosis of subclinical dysfunction. Minor dysfunction (subclinical hyperthyroidism) may become clinically significant in some patients, especially in those with heart disease, who are particularly susceptible to minor changes in thyroid functionality.

AIT classification in pathogenic forms was performed taking into account several criteria (clinical, laboratory data, therapeutic response). Quantification of thyroid parenchymal vascularity by colour Doppler ultrasound represents an important tool in the assessment of these cases.

There is no consensus regarding the diagnostic criteria of thyroid dysfunction induced by AMD. A survey of European thyroidologists (affiliated to the European Thyroid Association) and thyroidologists from Latin America presented heterogeneous opinions, in part because of different iodine intake, and hence different reported incidences of thyroid dysfunction [35–37].

Since 74.4% of AIT patients, and 17% of those with hypothyroidism, presented arrhythmias, thyroid functionality should be evaluated in any patient who develops arrhythmias during AMD treatment.

Although serum FT_3 values were similar in both thyrotoxic arrhythmic and non-arrhythmic patients, TSH concentrations were significantly lower in those who developed arrhythmias. Several studies have confirmed that suppressed TSH is involved in triggering supraventricular arrhythmias [38–40]. The degree of TSH suppression is a major determinant in the occurrence of arrhythmias, since their prevalence is higher in hyperthyroidism compared to euthyroidism, but is similar in overt and subclinical hyperthyroidism [41–44].

Conclusions

In a cohort of 229 AMD-treated patients from an iodine-replete area, 38.4% developed thyroid dysfunction: 17.9% hypothyroidism and 20.4% thyrotoxicosis. The main risk factors for AMD-induced thyroid dysfunction are represented by previous thyroid pathology (diffuse goitre, nodular goitre, and antithyroid antibodies). Such cases require systematic monitoring. Most of the thyrotoxic patients presented the overt form, while in the hypothyroid group, the subclinical form prevailed. The AIT group was dominated by type 2 and mixed forms. Although the classification of AIT cases in pathogenic types is important in terms of the therapeutic approach, there are still many cases which pose complex diagnostic difficulties.

The daily dose, the duration of the treatment, and the cumulative dose of AMD do not represent risk factors for the development of thyroid dysfunction. The determination of serum AMD and desethylamiodarone concentrations does not offer supplementary benefits in the diagnosis and treatment of thyroid dysfunction.

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