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Follow-up study of autonomous thyroid adenoma treated with I-131

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Twenty seven patients with autonomously functioning thyroid adenoma (AFTA), clinically and laboratory euthyroid were treated with I-131. A acriterion for the therapy was the scintigraphic appearance of AFTA "hot", and suppressed TRH response of the patients. The mean weight of AFTA was 50.03 ± 28.5 g, administered radioactivity was 13.3 ± 6.1 MBq per g tissue, and estimated radiation was 262.2 ± 129.9 Gy. Examinations in the follow-up period of 2-36 months included clinical and laboratory testing, TRH test and thyroid scintigraphy.

After the therapy. AFTA became unpalpable in 14 (51.8 %) patients, decreased in 7 (26.0 %) and did not change in 6 (22 %). All patients remained euthyroid by all criteria, with normal TRH test in 26 (96 %) of them. Two months after the therapy, transitory suppression or exaggeration of TRH test, was found in 3 and 1 patient resp., but spontaneous restitution occurred later in all but one, where TRH remained suppressed (3.7 % of all). AFTA appeared cold on the scan of 92.6 % of the treated patients. There was no hypothyroidism after the therapy. This and the achievement of ablation or reduction of the nodules in most of the patients, support the opinion that patients with AFTA and suppressed TRH test, even when euthyroid, should be treated with I-131.

Key words: thyroid neoplasms; adenoma-therapy; iodine radioisotopes; follow-up studies

Introduction

Plummer's disease is a thyroid disorder in which a part of the tissue is functioning autonomously and the rest of the gland is normally responding to feedback mechanisms. It is presented by a spectrum of structural and functional abnormalities which include solitary or multiple nodules, or numerous autonomous centers, and autonomous production of hormones in normal or excessive quantity.[1,2] The last is crucial for the clinical presentation of the disorder. When an autonomously functioning thyroid adenoma (AFTA) produces clinically overt hyperthyroidism, the therapy should be radically-surgical or with radio iodine, sometimes after a short-lasting medicamentous treatment.[2]

The treatment of AFTA in euthyroid patients rises many questions: is it necessary, in which cases and when, and what kind of therapy? Euthyroid clinical picture may be associated with different biological behavior of AFTA: compensated or decompensated, i.e. scintigraphically presented as isofixant or hiperfixant – "warm" or "hot" nodule, comparing to surrounding tissue.[3] Normal serum levels of T4, T3 and even TSH, may be associated with a suppressed response to TRH stimulation as a first sign of disorder.[3] Keeping in mind the slow evolution of AFTA and the possibility of spontaneous destruction of adenomatous tissue[4,5] many clinicians hesitate to choose a radical therapy. But the follow-up studies of many cases show steady progression of the disease in some patients, which may cause heart damage,[5,6] and Belfiore et al.[7] found that it happened in a higher percent of patients from

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iodine deficient regions than in those from other regions.

Here we present results of radioiodine treatment of euthyroid patients with AFTA and our attitude to that problem.

Material and methods

The study includes 27 patients with AFTA, clinically, euthyroid, who were treated with I-131 and subsequently followed-up. The diagnosis of AFTA and evaluatiion of clinical status were based on clinical, laboratory and scintigraphic examinations. Biologic behavior of AFTA was assessed by TRH-test response, as the serum thyroxine (T4) and triiodothyronine (T3) were in normal range. The therapy was accomplished by oral application of radioiodine dose, calculated according to the weight of AFTA and 24h-uptake of I-131. Follow-up evaluation included clinical and laboratory estimation of the thyroid function (T4 and T3 determination, TRH response), as well as scintigraphy of the gland.

A group of 20 patients who were healthy and with palpatory and scintigraphically normal thyroid, were tested for TRH response. They were considered as a control group in this study.

T4 and T3 were determined with RIA (kits produced by "Vinca", thyrotropine (TSH) in serum was determined with IRMA (CIS) (first generation). Normal values for T4 in T3 serum concentrations: 64–160 nmol/L resp. 1,5–3,4 nmol/L. Thyroid scintigraphy was performed mostly with I-131, after 24h of an oral dose of 1850 KBq, or with 800 MBq of Tc-99 m, 30-40 minutes after i.v. application. The weights of the nodules were determined by calculating their volumes as ellipsoids (diameters were measured by the scintigraphic imaging of the gland). This method had been proven by comparing the weights of operated nodules with calculated ones by their scans[8] (before introduction of ultrasound measurement). TRH test was performed by i.v. application of 200 µg Relefact TRH (Hoechst, AG) and serum TSH was determined in 0,30 and 60 min. after the application.

Results

Only two of the patients with AFTA were men (7 %), so that women/men ratio was 12,5/1. Age of the patients was 36–72 years, mean 53.48 ± 7.96, and the age of the control patients 40.38 ± 10.89 years. In 23 (85 %) patients there was a solitary nodule and in 4 (15 % of all) there were 2 nodules. The nodules in all patients were "hot" by scintigraphy and surrounding tissue was completely suppressed. Most of the patients were clinically normal and some of them only with mild and common complaints, as slight nervousness of fatigue. T4 na T3 serum levels were in normal range, but their mean values were statistically higher that in controls (Figure 1). TSH values were in normal range as well, ranging 0.5–0.4 µU/ml. TRH test was abnormal – unresponsive in all: no increase of TSH serum level was recorded after 30 or 60 min. of TRH injection, or the increase was minimal, not exceeding 1.5 µU/ml over basal level in 13 patients. As a normal response to TRH stimulation (positive response) it is considered an increasing of TSH level after 30 min. or more than 3 but less than 25 µU/ml, a criterion accepted by many authors.[3, 6, 9, 10] TRH test in the contol group showed an average elevation of TSH of 10.81 ± 4.2 µU/ml.

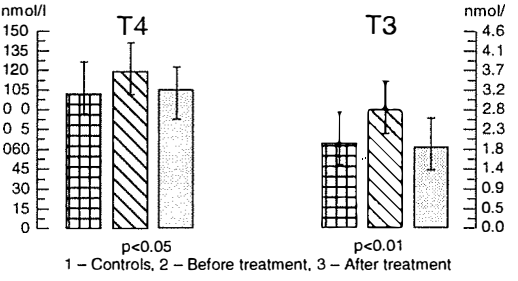

Figure 1. T4 and T3 in CONTROLS and in AFTA BEFORE AND AFTER I-131 TREATMENT

The data on the weights of AFTA and the applied radiotherapy are given on Table 1. The follow-up period after the therapy was 2–36 months (mean 14.1 ± 12.0).

Table 1. I-131 Treatment of autonomously functioning thyroid adenoma (AFTA), 27 patients.

	Mean ± SD	Range
Weight of AFTA (g)	50.0 ± 28.5	19–32
24h I-131 uptake	44.5 ± 12.1	27–78
Dose of I-131 (MBq)	1090.8 ± 244.2	740–1850
I-131/g AFTA (MBq)	12.1 ± 6.1	3.4–23
Radiation in AFTA (Gy/g)	262.2 ± 129.8	73.5–508

The clinical state in all patients remained euthyroid. The change of the size and scintigraphic appearance of AFTA is presented on Table 2. T4 and T3 levels decreased and although remained in normal range, their mean value, did not differ significantly from that of the control group (Figure 1).

Table 2. Follow-up of 27 patients with AFTA: findings of palpation, thyroid scintigraphy and TRH test (after the therapy).

	Number of patients	% of all
Reduction of AFTA size (by palpation):		
Not palpable any more	14	51.8
Reduced in size	7	26.0
Remained unchanged	6	22.2
Scintigraphic appearance:		
Cold nodule	25	92.6
Isofixant nodule	2	7.4
Hot nodule	0	0
TRH – Test:		
(Elevation of TSH levels – 30 min.)		
Normal (3–25 μU/ml)	26	96.3
Negative (3 μU/ml)	1	3.7

TRH test was performed in the follow-up period in all patients, at different times. It was normal in 22 of them and abnormal in 4: in 3 it was negative (increase of TSH less than 3 μU/ml at 30 min.), and in one, basal TSH was elevated and the test was exaggerated (Table 3). These patients were tested two months after the therapy, as were other 9 patients whose TRH test was normal. Repeated testing of those with abnormal test after 4–36 months, did not show abnormality in three of them and only one patient had a suppressed TRH response, even after 36 months. The nodule of the patient weighted 132 g and it received a lower radiation doses (86.5 Gy), but in spite of that, the nodule became unpalpable and "cold" on scan.

Table 3. Patients with abnormal TRH response two months after I-131 therapy.

Pat. No.	I-131 dosis	Radiation	No. month after I-131	TRH test	TSH (μU/ml)	
	(MBq/g)	(Gy/g)		Basal	30 min.	60 min.
J.D.	10.5	227.0	2	0.5	3.4	1.9
			22	3.2	10.4	8.1
M.A.+	4.0	86.5	2	0.5	0.6	0.6
			36	2.3	3.8	3.3
J.S.	3.6	77.9	2	2.4	5.1	4.5
			15	1.6	12.7	9.7
G.S.	14.3	309.0	2	16.0	46.0	40.0
			36	0.5	11.8	8.8

+ – the patient with persistent suppressed TRH response

Discussion

It is generally accepted that AFTA which causes hyperthyroidism should be treated radically – by surgical or radioiodine treatment. The data of many studies show that relapses and hypothyrosis after the treatment are very rare, in contrast to Graves' disease, where they occur in much higher percent.[2,5,10,11] The treatment of euthyroid patients with AFTA (solitary or multiple) is a matter of individual consideration, depending on different factors.[12] Since the early and later application of TRH test, has shown that it can discover subclinical hyperthyroidism[6,9,10] and so to help in decision-making for therapy. Discovering a disturbed thyroid function at its very beginning by TRH-test, is not of pure academic interest. Correcting it, an overt thyrotoxicosis may be prevented (which in older age is usually oligosymptomatic, manifested as a heart disease). Although progression of euthyroid AFTA to toxic nodule and hyperthyroidism is slow and not very frequent,[4,11] we observed it in 35 out of 181 euthyroid patients, followed-up during a period of 0,5–15 years, with statistical probability of 6,65 % to become hyperthyroid.[5] At last, one can not exclude the possibility of "Tissue hyperthyroidism" although not proved by laboratory findings.

All of our patients were euthyroid, with serum concentrations of T4, T3 and TSH in normal range (although statistically higher than in controls), but TRH test and scintigraphy revealed abnormal biological behavior of AFTA. Even in that case one may pose the question of the reason for therapy. Treatment of clinically and laboratory euthyroid patients if they are not young and their AFTA is large, is recommend by McConahey.[12] Our choice of radioiodine treatment for these patients was not wrong by our consideration, which could be supported by the results of the therapy:

– all treated patients remained euthyroid, with restituted physiological regulation of the thyroid, but one. None of the patients became hypothyroid. One patient who showed a transitory, subclinical hypothyroidism (exaggerated TRH response), recovered spontaneously.

– ablation of AFTA was achieved with lower doses of I-131 than those we[5] or other authors[11,13] usualy use for treatment of AFTA in hyperthyroid patients.

– the percentage of markedly reduced nodules is very high (77.8 % of all), so that this therapy offers also an esthetic effect and possible relief of com-

pressive effect of AFTA (if it were present). So, these effects, otherwise expected from surgical treatment, may be achieved by radiotherapy, without surgical risks.

A support of our approach to radioiodine treatment of euthyroid patients with AFTA, we found also in the excellent study of 87 thyroidectomized patients with Plummer's disease by Wiener.[14] He found in the follow-up period an unexpectedly high percent of postoperative thyroid autonomy in the residual tissue and this suggested that radioiodine treatment could be more effective that surgical treatment.

The amount of administered radioactivity is a matter of consideration in many studies. Although there is some relation between the dose and the success of the therapy (i.e. the incidence of hypothyroidism and failure of the therapy,[11–13,15] many authors,[11,12,15] found that the incidence of hypothyrosis is not related to the dose per gram of nodular tissue. By their experience, for its prevention is the most important: the scintigraphic appearance of the extra nodular tissue before the administration of I-131 should be sufficiently suppressed, with minimal iodine uptake. We agree with them and all of our patients were scanned shorlty before the therapy.

The finding of temporary exaggerated TSH response after the therapy in one patient, was surprising. It may be supposed that the suppressed extranodular tissue which was functioning below its normal capacity before the therapy, need more time for its functional recovery. There is a possibility that extranodular tissue was moderately irradiated and is in temporary hypofunction. These both possibilities do not exclude each other.

It is more difficult to explain the persistence of suppressed TSH response after the therapy. At two months after the therapy maybe the effect of radiation was not completed yet, but in the case when the nodule became cold, long time after the therapy the finding is unusual. As a coincidence of Grave's disease and AFTA in the same gland has been reported[16] it may be supposed that a thyroid autonomy of surrounding tissue developed during post-treatment period.

Our experience from this study is that examinations of clinically euthyroid patients with AFTA should be completed with TRH-test (or ultrasensitive measurement of TSH which is in use nowadays) and if it is suppressed the therapy may be taken in consideration.

Conclusions

1. AFTA decompensated on scan could be treated if TRH test is negative, in spite of euthyroid clinical and laboratory findings.

2. Radioiodine therapy is effective in curing the autonomy and very often in reducing the size of the nodules in doses of 3.4–23.0 MBq per g AFTA tissue.

3. About two months after the therapy a normal TSH response is achieved in most of the treated patients. Only in few patients it restores later and for evaluation of therapeutic effect TRH-test should be repeated.

4. Hypothyroidism after I-131 treatment of Plummer's disease is very rare, even in euthyrotic patients with AFTA.

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