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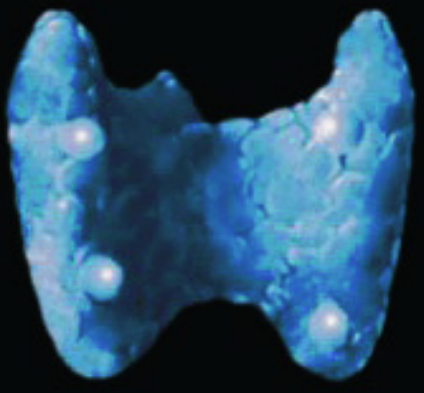

Journal of the Indian Thyroid Society

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Thyroid Research and Practice

Journal of the Indian Thyroid Society

***Editorial Office**: Department of Endocrinology, Amrita Institute of Medical Sciences, Elammakara PO, Cochin - 682026, Kerala.*
Tel : 0484-2802025. Fax : 0484 - 2802020. E-mail : adwa@aimshospital.org

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Thyroid Research and Practice

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The Indian Thyroid Society (ITS) is a registered society (Reg. No : ER 450/2003, dated 28.5.2003) founded in 2003.

The society aims to provide a forum for all surgeons, endocrinologists, nuclear physicians and physicians with a special interest in thyroidology.

The journal will publish original articles, reviews, case reports and other articles of interest to doctors interested in thyroidology.

Queries regarding the submission of the manuscript, subscription to the journal or membership to the society may be addressed to: The Editor, Thyroid Research and Practice, Indian Thyroid Society, Regd Office: Dept of Endocrinology, Amrita Institute of Medical Sciences,Cochin-682026, Kerala

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Editorial

Thyrotoxic myopathy: a disease in search of a diagnosis?

A G Unnikrishnan*, S Bhaskaran*, C N Buva, H kumar***, R V Jayakumar******

* Assistant Professor,
** DNB Trainee,
***Consultant and Head,
****Professor
Department of Endocrinology,
Amrita Institute of Medical Sciences,
Elamakkara PO,
Cochin-682026.

Corresponding Author :
A G UNNIKRISHNAN

E-mail:
unnikrishnanag@aimshospital.org

Thyroid hormones have important actions on the metabolism of skeletal muscles, an effect possibly related to the actions of these hormones on skeletal muscle gene expression.[1] Hyperthyroidism is associated with a high metabolic rate, muscle protein breakdown, and weight loss. The spectrum of muscular weakness in hyperthyroidism essentially encompasses four disorders: thyrotoxic myopathy, thyrotoxic periodic paralysis, extra-ocular muscle involvement, especially associated with thyroid-associated orbitopathy and the last being a disorder of the neuromuscular junction, myasthenia gravis. Among these disorders, the generalized form of thyrotoxic myopathy is the commonest, the disorder that is most directly linked to thyroid dysfunction and also the most responsive to the normalization of thyroid function.

Thyrotoxic myopathy is quite common, seen in about 60-80% of subjects with thyrotoxicosis.[2,3] Common presenting symptoms include fatigue, weakness and cramps.[4] Very characteristically, the disease involves the pectoral and the pelvic girdle muscles. The iliopsoas and the quadriceps are among the commonly involved muscles, and often the weakness is not extremely severe enough to cause a total paralysis.[5] In these muscle groups, weakness and wasting is often noticed, and this is usually symmetric. Fasiculations are rare, but have been described. Wasting of the temporalis and interossei may be seen in many patients, and in severe cases, there is generalized skeletal muscle wasting. Serum creatinine kinase levels are normal, and do not correlate with the severity.[5] Electromyography is usually normal. It is possible that severe degrees of involvement are becoming less common, probably owing to earlier diagnosis. More and more cases of focal muscular involvements are being reported, especially involving the bulbar and respiratory muscles, especially the diaphragm.[6,7] Muscle weaknesses precedes the onset of dysphagia, and unlike the classic thyrotoxic myopathy, electromyography often shows a myopathic or a neuropathic pattern. As a

cause of dysphagia, oropharyngeal muscle weakness, rather than esophageal dysmotility, is the likely factor involved. Aspiration pneumonia is a dreaded complication of this illness.[6]

More interesting is the role of respiratory muscle involvement in thyrotoxicosis. Dyspnoea is a common complaint in thyrotoxic subjects, is seen in more than 80% of subjects.[7] Dyspnoea could arise from cardiac failure, increased ventilatory drive, airway resistance, reduced lung compliance, tracheal compression by a goiter or respiratory paralysis. The diaphragm is the major inspiratory muscle and accounts for about two-thirds of the tidal volume. It has been reported that diaphragmatic muscle weakness could be an important factor contributing to breathing difficulties in these subjects.[7] This study reported diaphragmatic weakness in 96% of thyrotoxic subjects and also found that it is greatest during a maximal respiratory maneuver. Carbimazole therapy led to significant improvements in muscle weakness.

An important feature of thyrotoxic myopathy is that it rapidly responds to restoration of a euthyroid state. In a prospective follow up study of subjects with hyperthyroidism, all muscular symptoms disappeared within an average period of 3 months, and complete restoration of power occurred in all subjects at the end of one year.[5] Thyrotoxic subjects with bulbar and respiratory muscle weakness also respond promptly to the restoration of a euthyroid state.[6,7] Therapy with beta-blockers can partially improve generalized weakness in thyrotoxic subjects. This has led authors to hypothesize that both thyrotoxic and adrenergic effects mediate muscle weakness in these subjects.[8] This is however controversial.

The benefits on thyrotoxic myopathy with therapy could relate to a direct improvement in the muscle mass. Indeed, in an intensive study of body-composition parameters (muscle area, muscle strength, body composition and substrate metabolism) of five subjects with hyperthyroidism, the same parameters were reassessed at follow up to measure the changes that result when a thyrotoxic subject becomes euthyroid.[9] The authors reported that over the course of therapy, fat mass and lean body mass (assessed by bioelectrical impedance analysis) increased significantly and energy expenditure decreased. Thigh muscle area (assessed by computed tomography) improved by 24 % and arm muscle strength (assessed by means of a dynamometer) improved by 48 %. Overall, the authors concluded that muscle volume diminishes by about 20% in thyrotoxicosis, while muscle strength falls by about 40%, and suggest that about five to nine months of therapy might be needed before normal muscle mass and function are re-established.[9]

With the diagnosis of thyrotoxicosis being made earlier and earlier, it is possible that subjects could present with myopathy alone. It is important to look for subtle findings that suggest myopathy, as this may facilitate an earlier diagnosis. Also, it is important to clinically assess the pattern and degree of myopathy in every patient, because this is a reversible marker and its improvement can suggest a favorable clinical response.

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Original Article

Profile of Graves' disease in a tertiary hospital in Northern India and treatment with medical therapy

B Kulshreshtha*, R Khadgawat, G Kumar***, A C Ammini******

Abstract :

The present study is a two year retrospective analysis of Graves' disease patients who presented to the AIIMS Endocrinology outpatient department during January 2002 to December 2003. Of 214 patients with Graves' disease, 130 were females and 84 males. The average age at the onset of disease was 34.8 ± 11.9 years (11-70 years) and the average duration of the disease was 8.4 ± 6.5 months. Weight loss, palpitations, diaphoresis and tremulousness were the most common presenting complaints. A goitre of varying grades (Grade 1=32.6%, Grade 2=58.3%) was present in 85.2% of the patients. An infiltrative ophthalmopathy was present in 44 patients and pretibial myxedema was present in one patient. Of 214 patients, 15 patients were advised surgery, 42 patients were advised radiotherapy and rest were put on medical therapy. Patients with a minimum follow-up of four months on carbimazole were included for analysis. The patients followed up for an average period of 8.6 ± 4.2 months at mean follow-up intervals of 2.7 ± 1.7 months. An initial euthyroid state could be achieved (82.9%) and maintained in a majority (75.6%) of patients. The average dose and duration to achieve euthyroidism was 30.05 ± 0.8 mg and 3.2 ± 2.4 months respectively. Amongst 34 patients who achieved euthyroidism, 19 patients were initiated on a 30 mg dose, 6 on a 20 mg dose and 5 patients were initiated on a 45 mg dose. The average duration to become euthyroid was similar (2.2 ± 1.1, 3.5 ± 2.6 and 2.4 ± 1.1 months respectively) with the three treatment doses used (p value=0.65). Conclusion- We conclude that medical therapy is an effective means to achieve and maintain euthyroidism. Low dose of carbimazole is as effective as the higher dose in achieving euthyroidism.

Key words: Graves' disease, Medical therapy, Carbimazole, Thyrotoxicosis.

* Endocrinologist,
** Assistant Professor,
**** Professor,
Department of Endocrinology and Metabolism,
***Biostatistician,
All India Institute of Medical Sciences, New Delhi-110 029.

Corresponding Author :
AC AMMINI

Introduction

Graves' disease is a common cause of thyrotoxicosis. The three available options for treatment include antithyroid medications, surgery and radioiodine depending on various

indications. According to a nationwide survey conducted to determine the trends in management of Graves' disease amongst leading thyroidologists in India, the majority preferred antithyroid drugs as the mainstay of treatment. [1] There are no set guidelines regarding the initiation or maintenance doses of antithyroid medications and the duration of the therapy.[2] In the present study, which is a retrospective analysis of Graves' disease patients, we analysed the profile of Graves' disease and trends of management with the medical therapy in our clinic. Based on the results, we tried to analyse the optimum initiation and maintenance doses and the time required by the patients to become euthyroid.

Study design-

The present study is a two-year retrospective analysis of thyrotoxic patients who presented to the AIIMS Endocrine outpatient department during January 2002 to December 2003. During this period 18,700 new patients registered in the OPD and of them 312 (1.67%) had thyrotoxic disorders. Of 312 patients, 214 had Graves' disease, 35 Toxic Nodular Goitre and 13 Thyroiditis (Table 1). In 48 patients no conclusive diagnosis could be made due to paucity of clinical data and lack of follow-up .The diagnosis of Graves' disease was based on the clinical and biochemical profile and Radioactive Iodine Uptake (RAIU). In the absence of RAIU, a diagnosis of Graves' disease was considered in patients with a long duration of thyrotoxic symptoms for more than 6 months, requirement of antithyroid medications over a prolonged period and presence of an infiltrative ophthalmopathy. The data was entered in microsoft excel version 2000 and analysed using EPPINFO Version 6.04 d and SPSS Version 7.5. The statistical techniques used for analysing this data were independent student t-test and one way Anova with multiple range tests. Besides this, Mann Whitney and Kruskal Wallis wherever applicable was also used. P- value less than 0.05 was considered significant.

Results-

Of 214 patients with Graves' disease, 130 were females and 84 males. Many patients had been on antithyroid medications for variable duration at presentation. 146 presented in a thyrotoxic state, 52 in a euthyroid state and 16 in a hypothyroid state. 18 patients were less than 20 years of age at presentation while 15 patients were more than 60 years at presentation. The average age at the onset of disease was 34.8 ± 11.9 years. While the earliest age at presentation was 11 years , a 70 year old male presented with relapse of thyrotoxic symptoms after

Table 1. Patients presenting to AIIMS from Jan 2002– Dec 2003

Diagnosis	Frequency	Percentage
Graves'	214	69
Thyroiditis	13	4.2
Toxic MNG	35	11.3
Toxic adenoma	1	0.3
Iatrogenic	1	0.3
No diagnosis	48	15.5
Total	312	100

Table 2. Baseline characteristics of patients with Graves' disease

Characteristics	Mean values ± SD
Age (years)	37.29 ± 12.55
Weight (kg)	54.4 ± 11.7
Sex	130 F: 84 M
Age at onset (years)	34.8 ± 11.9
Duration of disease (months)	33.2 ± 58.6.
Duration of symptoms (months)	8.4 ± 6.5,
Goitre present	85.2 %, Grade 1 - 23.8%, Grade 2 - 42.5%
T_4 (nmol / L)	223.2 ± 31.6
TSH (mU/L)	0.60 ± 0.64
RAIU 2	34.6 ± 18.5(43)
RAIU 24	56.3 ± 16.7

Number of patients in parenthesis ( )

a disease free interval of 43 years. Patients had been symptomatic for an average duration of 8.4 ± 6.5 months. 14 patients presented with a relapse of thyrotoxic symptoms. The median interval for the second relapse was two years (mean - 8.64 ± 12.22 yrs). Table 2 provides the baseline characteristics in patients with Graves' disease. A majority of patients (122) presented during the summer months compared to 92 presenting during the winter months.

The most common symptoms were weight loss, tremors , diaphoresis , palpitations , fatigue and diarrhea. Table 3 gives the frequency of thyrotoxic symptoms in the decreasing order of frequency. One patient presented in a thyrotoxic storm. Cardiac complications included two cases of atrial fibrillation and one case of cardiac failure. Infiltrative ophthalmopathy was present in 44 (20.5%) patients and pretibial myxedema was present in one patient. Compressive symptoms were present in 4 patients. Other comorbid conditions included diabetes in 3 patients , osteomalacia in 3 patients , myasthenia gravis in two patients and periodic muscular paralysis in one patient .

Hyperpigmentation was found in seven patients- 3 females and 4 males. Two of these were diagnosed to have cortisol insufficiency. Of these two patients, one patient survived a cardiorespiratory arrest after stopping the medications . The average age of the patients presenting with hyperpigmentation was 28.5 ± 2 years and these patients had been symptomatic for an average duration of 5.08 ± 3.98 months . A grade 2 goitre was present in 6 out of 7 hyperpigmented patients.

Goitre was present in 156(85.2%) patients- Grade 1 goitre- 51(32.6%), Grade 2 - 91(58.3%). In 14 patients the grade of goitre was not mentioned in the files.

Treatment advised

Of 214 patients, 15 patients were advised surgery. Reasons for surgery were cold nodule, compressive symptoms, relapse, age less than 30 years, a long duration of the disease, young men and women planning to have children, poor drug

Table 3. Frequency of thyrotoxic symptoms in decreasing frequency*

Symptoms	Frequency (Percentage)
Weight loss	66 (45.2 %)
Tremors	52 (35.6 %)
Diaphoresis	37 (25.3 %)
Diarrhoea/increased gastrocolic reflux	26 (17.8 %)
Palpitations	23 (15.8 %)
Fatigue	23 (15.8 %)
Irritability / psychosis	21 (14.4 %)
Heat intolerance	20 (13.7 %)
Restlessness	13 (8.9 %)
Dyspnoea	10 (6.8 %)
Hyper-pigmentation	6 (4.1 %)
Compressive symptoms	4 (2.7 %)

* This is a retrospective analysis, therefore the given symptoms may be an underrepresentation of the data.

compliance, severe ophthalmopathy and cosmetic reasons. 42 patients were advised radiotherapy after attainment of a euthyroid state with antithyroid drugs, while 149 patients were either initiated or continued on medical therapy with carbimazole 20-45 mg daily.

Response to medical treatment in relation to varying doses of carbimazole

Patients with a minimum follow-up of four months on antithyroid medication (carbimazole) were included for analysis. The patients followed up for an average period of 8.68 ± 4.2 months at mean follow-up intervals of 2.75±1.77 months. 34 of 41(82.9%) patients achieved an initial euthyroid state. The average dose and duration to achieve euthyroidism was 30.05 ± 0.8 mg and 3.2 ± 2.4 months respectively. Majority of these patients could further maintain a euthyroid state on an average carbimazole dose of 15mg.

Amongst 34 patients who achieved euthyroidism, 19 patients were initiated on a 30 mg dose ,6 initiated on a 20 mg dose and 5 patients were initiated on a 45 mg dose. Remaining 4 patients who were initiated on a 25 or 60 mg dose. Table 4 provides the response to different doses of carbimazole. The average duration to become euthyroid was 2.20±1.1, 3.5±2.6 and 2.4±1.1 months respectively in the three treatment groups (difference was not statistically significant).The three groups were comparable with respect to baseline characteristics i.e. age, sex and grade of goitre except duration of symptoms which was least in the 20 mg group and maximum in the 45 mg group (3.3 ± 1.9 and 20 ± 6.9 months respectively). Though a history of carbimazole intake was present in 8 patients in the 30 mg group and 1 patient in the 45 mg group , the dose and duration of carbimazole taken during this period were added to the total duration to achieve euthyroidism.

Table 4. Different doses of carbimazole and response to treatment

Parameter	Doses of carbimazole			
	20 mg(n=6)	30 mg(n=19)	45 mg(n=5)	P value
Age (years)	36.2 ± 11.9	37.1± 9.7	28.6 ± 8.3	0.24
Sex F ; M	4 ; 1	13 ; 7	2 ; 3	0.41
Duration of symptoms (months)	3.3 ± 1.9	9.3 ± 7.4	20 ± 6.9	0.02*
Goitre present	5 (83.3%)	18♣(94.7%)	4 (80%)	
Grade goitre(Grade 1;Grade 2)	3 ; 2	5 ; 10	1 ; 3	0.87
Duration for euthyroidism (months)	2.2 ± 1.1	3.5 ± 2.6	2.4 ± 1.1	0.39

* 20 mg vs 45 mg treatment group, P value < 0.05

♣ In 3 patients, grades of goitre were not known

Response to medical treatment in relation to different grades of goitre

Table 5 provides the response to treatment in relation to different grades of goitre size. The two groups were comparable in relation to baseline characteristics and the doses of carbimazole used. The duration to achieve euthyroidism was similar in the two groups (3.1 ± 2.3 and 3.4 ± 2.5 months, p value=0.31).

Course of treatment during follow-up

An initial euthyroid state could be achieved (82.9%) and maintained in a majority (75.6%) of patients. However, 7 patients developed an initial hypothyroid state. Five patients went on to develop thyrotoxicosis -3 after an initial euthyroid state and 2 after an initial hypothyroid state. In 3 patients, this thyrotoxic state was related to non compliance. In 2 patients, this thyrotoxic state was related to an inappropriate reduction in carbimazole dose when the physicians encountered a hypothyroid biochemical profile.

Patients who developed an initial hypothyroid state

A significant number of patients (17.07%) went on to develop hypothyroidism. In 4 of these7 patients, development of hypothyroidism was related to a poor follow-up i.e. these patients followed up after longer intervals. The average dose and duration to develop hypothyroidism was 28.0 ± 9.18 mg and 7.6 ± 7.6 months respectively. Two of these patients deserve a special mention - One of these was a 33 year old female patient who had thyrotoxic symptoms for 4 months. She developed hypothyroidism within one month of initiation of 25 mg of carbimazole dose. This patient had a lower 2 and 24 hour RAIU (2.6 and 37.2%). Another patient, a 25 year old female, symptomatic for 5 months, developed hypothyroidism after 7 months of carbimazole (20 mg for 1 month and 15 mg for 6 months). This patient also had a lower 2 and 24 hour RAIU of 7.6% and 31.8% respectively.

Discussion

In the present study, a large majority of the thyrotoxic patients had Graves's disease (69%). Studies from the West also report

Table 5. Grades of goitre and response to treatment

	Grade1 goitre (n = 9)	Grade 2 goitre (n = 17)	P value
Age at onset (years)	43.3 ± 11.6	35.7 ± 11.7	0.217
Sex F : M	4 : 3	10 : 5	0.97
Duration of symptoms (months)	8.3 ± 9.6	10.5 ± 7.9	0.6
Dose (mg)*	27.7 ± 8.7	31.1 ± 7.1	0.29
Duration (months)*	3.1 ± 2.3	3.4 ± 2.5	0.31

* indicates dose and duration of carbimazole for achieving euthyroidism

a similar frequency of 70-85% Graves' disease as etiology of thyrotoxic

Disorders.[2] While the females with Graves' disease clearly outnumbered the males in the present study(130 F : 84 M), this ratio was much less than the reported proportion of 5-8:1 from the west.[2] This discrepancy could be either due to regional differences or a reflection of poor medical accessibility by the underprivileged section of females in Northern India. Also, a tertiary institution may not be a perfect setting for assessing the true prevalence.

While most patients were either thyrotoxic or euthyroid when they presented to our hospital, 16 patients presented in a hypothyroid state. Four of these had stopped antithyroid medications for a reasonable length of time (2.8 ± 1.4 years). Such a natural progression of the disease from a thyrotoxic to a hypothyroid state is well known. Lamberg et al reported a 3.1% annual incidence of spontaneous hypothyroidism (2.5% subclinical hypothyroidism and 0.65% overt hypothyroidism) 4.85 ± 2.55 years after stopping the antithyroid treatment for Graves' disease.[3]

In 14 patients who presented with a relapse of thyrotoxic symptoms, the relapse occurred at a median interval of two years (mean 8.64 ± 12.22 years). Hedley et al studied the natural course of Graves' disease in 434 thyrotoxic patients followed up for a period of 10 years. They found that while the majority of relapses occurred in the initial 5 years (72-90%) depending on the T_3 suppressibility, an additional 10% of relapses occurred between 5 and 10 years.[4] Our study showed a similar trend, 78.5% relapses occurred in the initial 5 years and 14.2% relapses occurred between 5 and 10 years. However, 3 patients had a second episode of thyrotoxicosis 20, 23 and 43 years respectively. Such late recurrences have been reported earlier after disease free intervals of 15, 25 and 31 years.[5,6] However, to the best of our knowledge a 70 year old male presenting after 43 years of disease free interval is the longest reported relapse. There is a paucity of long term follow-up studies on thyrotoxic patients from India, however these late recurrences could be a reflection of poor iodine status in our country.

All the co-morbid conditions in the present study (diabetes, osteomalacia, myasthenia gravis and hypokalemic periodic paralysis and cortisol insufficiency) are well known associations of Graves' disease. Cortisol insufficiency is attributed to the increased clearance of cortisol in thyrotoxic patients.[7]

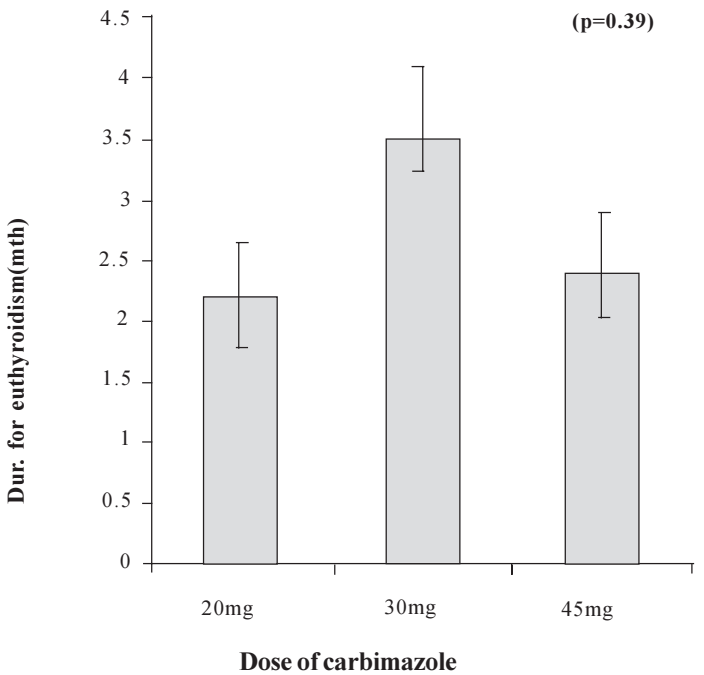
The present study demonstrated that the low dose of 20 mg carbimazole is as effective as the high dose of 45 mg in attaining euthyroidism. A similar response of equivalent efficacy and lesser side effects with 15-mg carbimazole dose as compared to 30 mg dose was reported by Shiroozu et al in their study.[7] They further supported their results with perchlorate discharge

tests performed one day after carbimazole treatment and found a similar efficacy of the low and high carbimazole doses in inhibiting organification. The time taken to attain a euthyroid state in our study was similar with the three treatment doses used (2.20 ± 1.1, 3.5 ± 2.6 and 2.4 ± 1.1 months respectively, p value =0.65). Shiroozu et al followed their thyrotoxic patients at regular intervals of 1-4 weeks and found comparable results. The apprehension that low doses may be associated with frequent relapses has been adequately addressed by a large number of studies showing futility of block replacement therapy in preventing relapses.[8,9,10]

The present study also showed that the time taken to attain euthyroidism was not influenced by the goitre size . Similar results were observed in Shiroozu study.[7] However Macfarlane et al found that patients with large goitres took longer to respond.[11] Such discrepant results could be due to different methods used to quantitate the goitre size, unsuitability of palpation as a method used to assess the goitre size and regional differences in the iodine status.

An unacceptably large proportion of our patients (17.07%) went on to develop hypothyroidism while on antithyroid medication. Though, in a majority of patients development of hypothyroidism was attributable to a poor follow-up, in a few patients development of a hypothyroid state could not be explained on the basis of large cumulative carbimazole doses used. Two of these patients described above, had a lower RAIU. Amongst the various parameters known to predict the relapse rate, a low initial RAIU and an early fall in the RAIU during therapy has been considered as one of the parameters predicting prolonged remission.[12] There is also a possibility that these subgroup of patients had a higher titer of thyroid binding inhibitory immunoglobulins as compared to thyroid stimulating antibodies.

Figure 1. Doses of carbimazole and response to treatment



We conclude that medical therapy is an effective means to achieve and maintain euthyroidism. A low carbimazole dose seems as effective as a high carbimazole dose in achieving euthyroidism. Our study supports the use of a small dose. However, given the small number of patents involved, a prospective study involving a larger number of patients is required to come to well defined conclusions.

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Basic Science Review

Effect of fluoride on thyroid functions: myths and facts

S K Das*, D M Vasudevan, S S Dey*****

Abstract

The widespread use of fluoride to reduce dental caries has aroused considerable controversy. Fluoride is toxic when consumed in excessive amounts. Industrial fluorosis is on the increase on a global basis. While some researchers have concluded that fluoride has no effect on the thyroglobulin content of the thyroid gland or the degree of iodination of thyroglobulin, others have shown that adverse changes occur with higher intakes of drinking water in endemic fluorosis areas or with fluoride treatment.

Keywords: Fluoride, Dental caries, Fluorosis, Thyroid, Hyperthyroidism

* Assistant Professor,
**Professor and Head,
Department of Biochemistry,
Amrita Institute of Medical Sciences,
Elamakkara P.O., Cochin 682 026

***Scientist,
Department of Physiology,
Dr. P. Siddhartha Institute of Medical Sciences,
Chinoutpalli, Gannavaram,
Krishna District, A.P. 521 286

Corresponding Author :
S K DAS

Introduction

Thyroid hormone is essential for normal brain development. Thyroid function can be altered by a very large number of chemicals usually found in the environment. They can produce thyroid dysfunction when they are absent from the diet, as in the case of iodine, or when they are present in the diet, as in the case of thionamides. Hyperthyroidism is a disorder of an over-active thyroid gland and is treated by reducing the body's metabolism rate. One of the lesser-known facts about fluoride (the "miracle" drug in your toothpaste and water) is that it has been used as a medication - not just for the prevention of tooth decay - but also for the treatment of hyperthyroidism.

Chemistry

Fluorine occurs naturally in the Earth's crust, water, and food as the negatively charged ion, fluoride (F^-). Fluoride is considered a trace element because only small amounts are present in the body (about 2.6 grams in adults) and because the daily requirement for maintaining dental health is only a few milligrams a day. About 95% of the total body fluoride is found in bones and teeth.[1] It is not generally considered an essential mineral element.

Table 1. Few fluoride-rich food items[3]

Food	Serving	Fluoride (mg)
Tea	100 ml (3.5 fluid ounces)	0.1-0.6
Canned sardines (with bones)	100 g (3.5 ounces)	0.2-0.4
Fish (without bones)	100 g (3.5 ounces)	0.01-0.17
Chicken	100g (3.5 ounces)	0.06-0.10

Sources

Water and food are the major sources of fluoride. The fluoride content of most foods is low (less than 0.05 mg/100 grams). Rich sources of fluoride include tea, which concentrates fluoride in its leaves and marine fish that are consumed with their bones (e.g., sardines). Food made with mechanically separated (boned) chicken, such as canned meats, hot dogs, and infant food also add fluoride to the diet.[2]

Fluoridated toothpastes add considerably to fluoride intake of children, especially young children who are more likely to swallow them. The major source of excess fluoride intake in this age group comes from swallowing fluoride-containing toothpaste.[1,3]

Absorption

Fluoride is absorbed in the stomach and small intestine. Once in the blood stream it rapidly enters mineralized tissue (bones and developing teeth). At usual intake levels, fluoride does not accumulate in soft tissue. The predominant mineral elements in bone are crystals of calcium and phosphate, known as hydroxyapatite crystals. Fluoride's high chemical reactivity and small radius allow it to either displace the larger hydroxyl (-OH) ion in the hydroxyapatite crystal, forming fluoroapatite, or to increase crystal density by entering spaces within the hydroxyapatite crystal. Fluoroapatite hardens tooth enamel and stabilizes bone mineral.[4]

Both calcium and magnesium form insoluble complexes with fluoride and are capable of significantly decreasing fluoride absorption when present in the same meal. However, the absorption of fluoride in the form of monofluorophosphate (unlike sodium fluoride) is unaffected by calcium. A diet low in chloride (salt) has been found to increase fluoride retention by reducing urinary excretion of fluoride.[1]

Recommended Dietary Allowance

Epidemiological investigations of patterns of water consumption and the prevalence of dental caries across different climates and geographic regions with different water fluoride concentrations in the United States led to the development of a recommended optimum range of fluoride concentration of 0.7-1.2 mg/liter or parts per million (ppm), with the lower concentration recommended for warmer climates where water consumption is higher, and the higher concentration for colder climates. Recommended Dietary Allowance (RDA), instead of Adequate Intake (AI) levels were based on estimated intakes (0.05 mg/kg of body weight) that have been shown to reduce the occurrence of dental caries most effectively without causing the unwanted side effect of tooth enamel mottling i.e. dental fluorosis.[3]

Disease Prevention

Dental caries (cavities and tooth decay)

Specific cariogenic (cavity-causing) bacteria found in dental plaque are capable of metabolizing certain carbohydrates (sugars) and converting them to organic acids, which can dissolve susceptible tooth enamel. If unchecked, the bacteria may penetrate deeper layers of the tooth and progress into the

soft pulp tissue at the center. Untreated caries can lead to severe pain, local infection, tooth loss or extraction, nutritional problems, and serious systemic infections in susceptible individuals.[5] But the mechanisms for preventing dental caries by fluoride are not entirely understood. It was believed that fluoride incorporated into the enamel during tooth development resulted in more acid-resistant enamel. But recent research indicates that the primary action of fluoride occurs topically (at the surface) after the teeth erupt into the mouth. When enamel is partially de-mineralized by organic acids, fluoride in the saliva can enhance the re-mineralization of enamel through its interactions with calcium and phosphate. In the presence of fluoride, re-mineralized enamel contains more fluoride and is more resistant to demineralization. In salivary concentrations associated with optimum fluoride intake, fluoride has been found to inhibit bacterial enzymes, resulting in reduced acid production by cariogenic bacteria.[5,6]

Adverse effects

Fluoride is a cumulative toxin. Fluoride is toxic when consumed in excessive amounts. The lowest dose that could trigger life-threatening symptoms is considered to be 5 mg/kg of body weight. Nausea, abdominal pain, and vomiting almost always accompany acute fluoride toxicity. Other symptoms like diarrhea, excessive salivation and tearing, sweating, and generalized weakness may also occur.[7]

Fluorosis is considered endemic in 15 states of India. In Kerala, the condition is reported to be endemic in the districts of Alappuzha and Palakkad.[8] It affects the homeostasis of bone mineral metabolism. The total quantity of ingested fluoride is the single most important factor, which determines the clinical course of the disease. A combination of osteosclerosis, osteomalacia and osteoporosis of varying degrees as well as exostosis formation characterizes the bone lesions. In a proportion of cases secondary hyperparathyroidism is observed with associated characteristic bone changes. Severe crippling forms of skeletal fluorosis are seen in pediatric age group too. Increased metabolic turnover of the bone, impaired bone collagen synthesis and increased avidity for calcium are features in fluoride toxicity. Osteosclerotic picture is evident when small doses of fluoride are ingested over a long period of time during which calcium intakes are apparently normal while osteoporotic forms are common in paediatric age group and with higher body load of the element. Alterations in hormones concerned with bone mineral metabolism are seen in fluorosis.[9]

Fluoride and Thyroid

Effects

Several authors postulated that goitrous states may be attributed to fluorine intake and conversely, that this element can be utilized in the treatment of hyperthyroidism.[10] Other investigators, however, could not reproduce these definite changes in the thyroid and thus the thyreostatic activity of fluorine is still questioned. The hyperfunctioning thyroid is a more sensitive structure than the normal gland. Few clinical studies are concerned with physiologic and toxic effects of fluorine over long periods.[11]

The increasing use of fluoride for prevention of dental caries poses the problem as to whether this halogen has antagonistic properties towards iodine, whereby it could hamper the success of iodine prophylaxis of endemic goitre. Burgi et al observed that fluoride does not potentate the consequences of iodine deficiency in populations with a borderline or low iodine intake.[12] Siebenhuner et al also concluded that fluoride had no effect on thyroglobulin content of the thyroid gland or on the degree of iodination of thyroglobulin.[13] Clay and Suttie suggested that young heifers could be fed up to 50 ppm of a soluble fluoride with no adverse effect.[14]

Although thyroid function and structure are purported to be unaffected by 1 ppm fluoride in drinking water,[12] adverse

changes occur with higher intakes in endemic fluorosis areas or with fluoride treatments. Increased dietary fluoride has resulted in thyroid enlargement,[15] reduced thyroid adenylate cyclase, and decreased blood thyroxine (T_4) and triiodothyronine (T_3).[16] Hypothyroidism and anemia have occurred not only with antithyroid medications but also with fluoride.[17]

Yang et al indicated that high iodine and high fluorine exert severe damage to human body.[18] Jooste et al indicated that a high fluoride level in the water, other than iodine deficiency, might have been responsible for goitres.[19] Iodine and fluorine do have mutually interacting effects on both goiter and fluorosis in the experimental mice.[20] Bobek et al found that fluoride administration caused decrease in thyroxine and triiodothyronine level in plasma, decrease in free thyroxine index values, and increase in T_3-resin uptake ratio.[21] Thus fluoride given continuously to the rats may influence the thyroid gland indirectly by changing thyroid hormone transportation in the blood.

The effect of fluoride on murine thyroid function and cerebellar development was studied by Trabelsi et al[22] who showed a decrease in body weight, a decrease in plasma free T_4, and reductions in the cerebellar and cerebral protein concentrations. Consistent histological changes were present in the cerebellum of the treated mice with the external granular layer being markedly reduced or absent, the Purkinje cell bodies being poorly differentiated and arranged in a single layer at the surface of the internal granular layer, and with more apoptotic Purkinje cells being present. Bachinskii et al concluded that excess of fluorine in drinking water was a risk factor for more rapid development of thyroid pathology.[23] Moderate functional changes of the hypophyseal-thyroid axis, not accompanied by clinical manifestations were observed in the blood of those engaged in fluorine production.[24] Elevation of calcitonin concentration in worker's blood indicated stimulation of thyroid gland parafollicular cells.[24]

Mechanism

Apart from the possibility of direct uptake of fluorine by the thyroid, another interesting hypothesis is that fluorine could have a mass-action effect on the uptake of iodine.[25] Under normal conditions the plasma fluorine level is about four times higher than the iodine level and therefore the action of fluorine upon thyroid physiology is not likely to be the result of simple competition between the halogens for receptor sites within the gland. The only evidence concerning the mode of action of fluorine upon thyroidal function relates to the direct reduction of the uptake rate of inorganic iodine. This interpretation receives further support from: the appearance of a goiter, clinical improvement after fluoride therapy, and recurrence of hyperthyroidism when iodine intake was simultaneously increased.[26]

Diagnosis and Therapy

Dental fluorosis is the most convenient biomarker of exposure to fluoride.[8] The mildest form of dental fluorosis is detectable only to the trained observer and is characterized by small opaque white flecks or spots on the enamel of the teeth. Moderate dental fluorosis is characterized by mottling and mild staining of the teeth and severe dental fluorosis results in marked staining and pitting of the teeth.

Intake of fluoride at excessive levels for long periods of time may lead to changes in bone structure known as skeletal fluorosis. The early stages of skeletal fluorosis are characterized by increased bone mass, detectable by x-ray. If very high fluoride intake persists over many years, joint pain and stiffness may result from the skeletal changes. The most severe form of skeletal fluorosis is known as "crippling skeletal fluorosis," which may result in calcification of ligaments, immobility,

muscle wasting and neurological problems related to spinal cord compression.

Serum parameters rarely help in the diagnosis. Kidney is the primary organ of excretion for fluorides.[9] Elevated urinary fluoride and increased bone fluoride content are indicators of fluoride toxicity. Fluorosis is a preventable crippling disease.[9] Indicators of the fluorine content in daily urine provide most of the information on changes of the fluorine amount in the body.[23]

No effective therapeutic agent is available which can cure fluorosis.[9]

Conclusion

Baumann and Metzger suggested that the thyroid has an affinity not only for iodine, but also for other members of the seventh periodic group of elements.[27] Several studies utilizing fluorine,[28] chlorine,[29] bromine,[30] astatine,[31] manganese,[32] technetium[33] and rhenium[34] have consistently demonstrated the ability of the thyroid to concentrate these elements in a ratio of greater magnitude than that measured in other tissues of the body.

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Case Report

Concurrent medullary and papillary carcinoma of thyroid : A rare combination

P V Pradeep*, P Jacob*, R C George*, S Vaidyanathan, A Nambiar***, A V Suseelan*****

Abstract

Different types of composite tumors have been described in the thyroid. Of these, a combination of tall cell variant of papillary and Hurthle cell carcinoma is one of the commonest one. We describe a rare case of medullary – papillary carcinoma of thyroid.

Key words: Collision tumor, Medullo-papillary carcinoma , Composite tumor

Introduction :

Collision tumors have been described in relation to various tumors. In thyroid malignancies, the tall cell variant of papillary with hurthle cell and the combination of medullo-follicular carcinoma have been described.[1] Medullary carcinoma of thyroid arises from parafollicular C cells and papillary carcinoma arises from follicular cells. Since the embryological origin of thyroid follicular cells is from the endoderm and the origin of parafollicular cells is from the ectodermal neural crest this poses an interesting question as to the common stem cell of origin of these tumors.

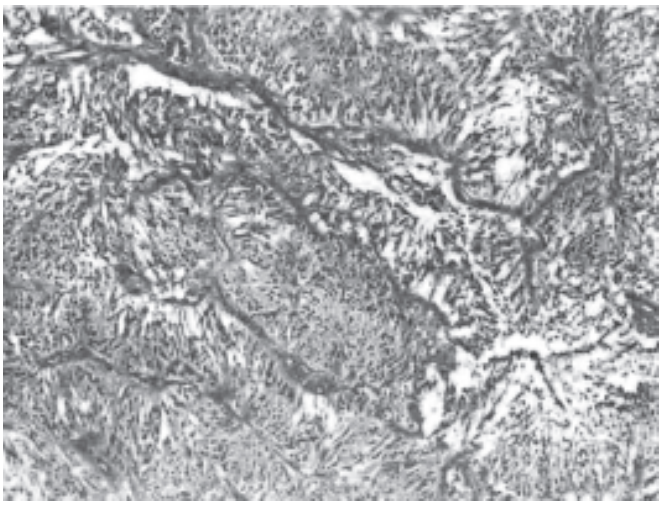
Clinical Details:

A 40 year old female patient reported to us with an asymptomatic solitary nodule of thyroid confined to the left upper pole of thyroid. FNAC performed suggested medullary thyroid carcinoma. There was no similar family history. Patient was assessed for features of MEN 2a and MEN 2b. She was normotensive. Her serum calcium and serum PTH levels were normal. Serum calcitonin levels were normal .USG neck showed two nodules both in the left lobe one at the upper and the other at the middle third of the gland. This was confirmed with a CT scan to rule out a concurrent parathyroid tumor in the neck .USG abdomen did not reveal any adrenal lesions.

* Assistant Professor,
**Professor,
Dept. of Surgery,
*** Pathologist,
Amrita Institute of Medical Sciences
Elamakkara P.O., Cochin 682 026

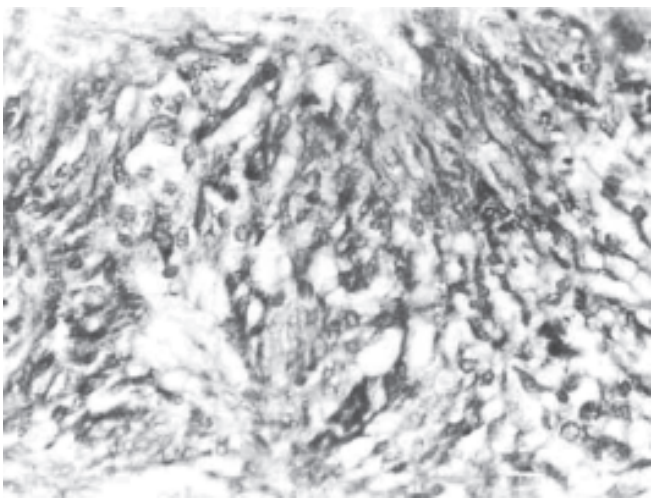
Corresponding Author :
S VAIDYANATHAN

Figure 1.Histology of nodule A (Medullary thyroid carcinoma)



At surgery two nodules were seen. The first nodule (A) was in the upper pole and second one (B) in the middle third of the left lobe, very close to the entry of the recurrent laryngeal nerve. The rest of the thyroid gland was normal. There were no enlarged neck nodes. Total thyroidectomy and central neck dissection were performed. Post operatively, patient had a smooth recovery.

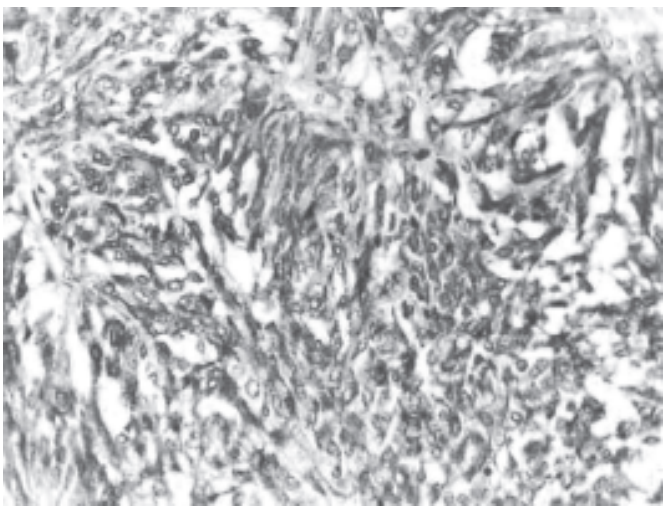
Figure 2. Calcitonin staining positivity (Nodule A)



Immunohistochemistry revealed nodule A as medullary thyroid carcinoma (Figure 1). It was 1.4 cm in size and it stained positive for both calcitonin and chromogranin (Figure 2 and 3). The nodule B was positive for papillary carcinoma (Figure 4). The size was 2 cm and it was negative for calcitonin and chromogranin and positive for thyroglobulin (Figure 5 and 6). No nodes were identified as being positive for either of these malignancies.

The patient was scheduled for a radioiodine uptake scan and ablation. He was eventually planned for long-term levothyroxine suppressive therapy.

Figure 3. Immunohistochemistry showing chromogranin stain positivity (Nodule A)



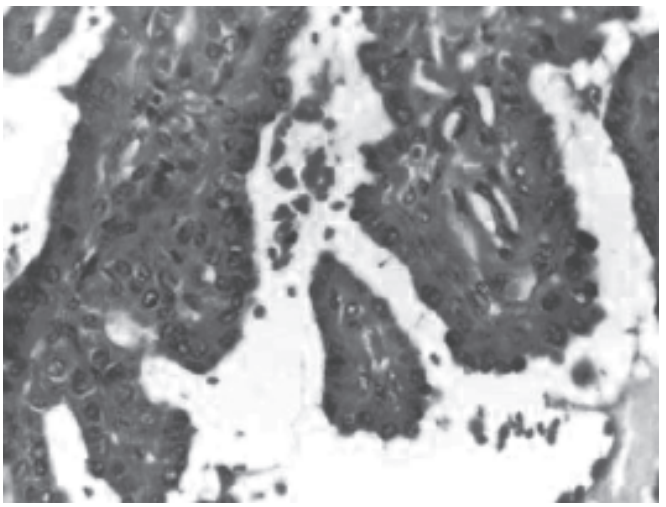
Discussion :

The thyroid gland is composed of two discrete functional components. Follicular epithelium and parafollicular C cells as well as each cell type may undergo malignant transformation. Immunohistchemical studies demonstrate that follicular cells produce thyroglobulin while parafollicular cells express calcitonin.[2]Various terminologies have been used to define these tumors like concurrent tumors,[3] mixed tumors,[4] composite tumors[4] and collision tumors.[3] The term 'Collision tumor' has

been reserved for metastasis of two tumor types into a single node.[3] Mixed tumor is one where one tumor type is identified histologically but dual differentiation can be appreciated on immunohistchemical studies and / or ultrastructural studies.[4] In composite tumors both the medullary and papillary component would be appreciated at the light microscopy level.[4]

It has been proposed that the tumor may originate from a common stem cell like the ultimobranchial body, since immunoreactivity for both calcitonin and thyroglobulin has been demonstrated in the ultimobranchial body.[5] A common

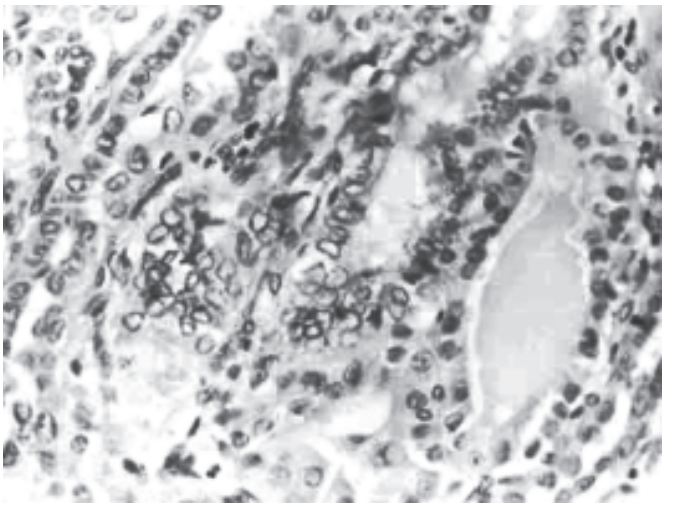
Figure 4. Histology, typical of papillary thyroid carcinoma (Nodule B)



tumorogenic stimulus for both follicular and parafollicular cells which stimulate neoplastic transformation of both the cell types was also suggested.[6, 7] Some authors have suggested that as papillary microcarcinoma being so common, this might be just a coincidence.

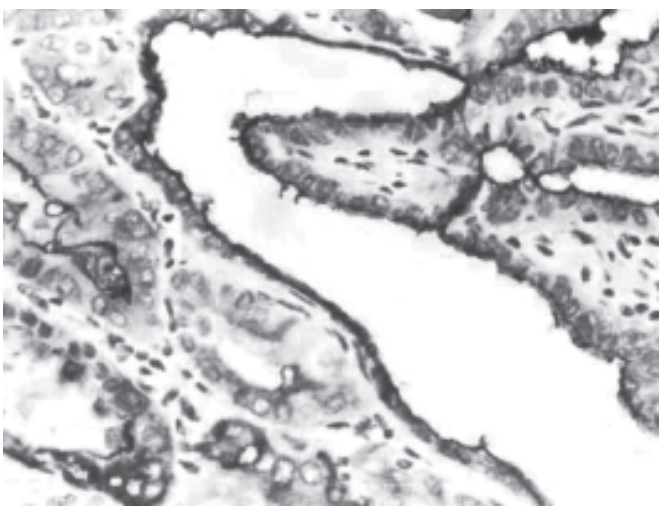
The general treatment policy will be to treat the worse tumor type. In general, female sex, age less than 40 years, tumor size < 3 cm, absence of lymph nodes in the neck, positive calcitonin

Figure 5. Staining negatively for chromogranin (Nodule B)



immunoreactivity and presence of amyloid are all good prognostic signs for the patient. Since our patient had all these characteristics she is currently under follow up. Follow up is done with periodic calcitonin, carcinoembryonic antigen, thyroglobulin assays and clinical examination.

Figure 6. Thyroglobulin stain positivity (Nodule B)



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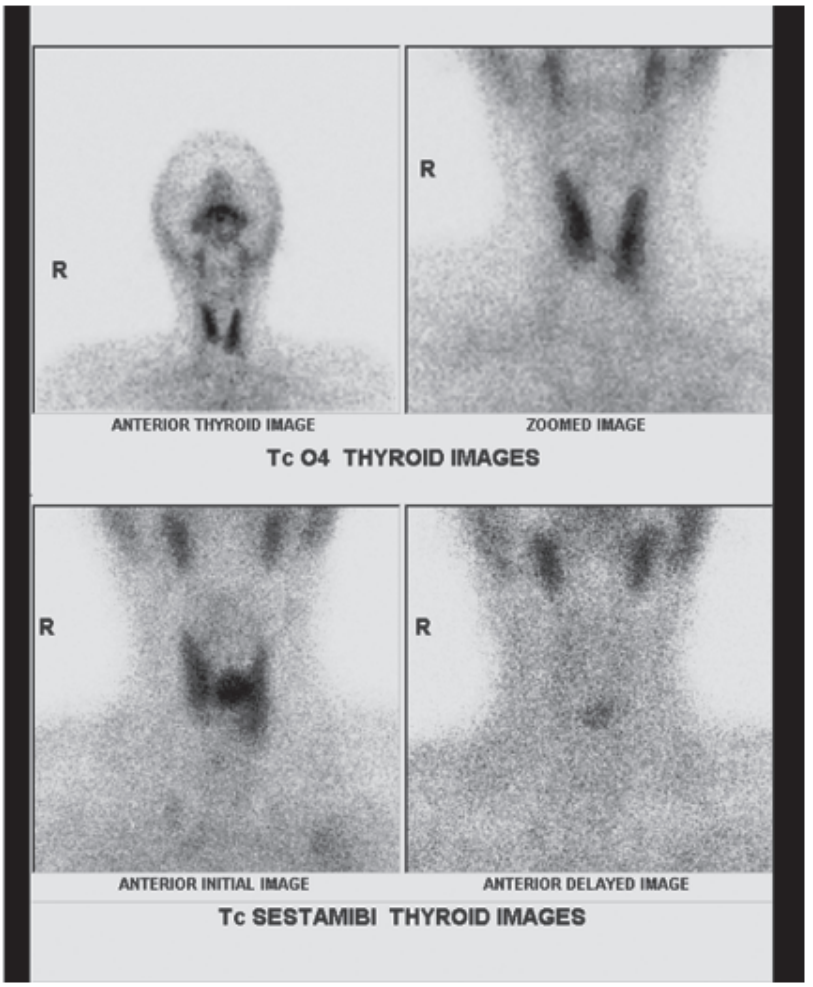
Thyroid Images

Compiled by P Shanmughsundaram, P S Sundaram
Department of Nuclear Medicine, Amrita Institute of Medical Sciences, Cochin.

42 year old male presented with solitary thyroid nodule of 2 years duration which was apparently asymptomatic. Thyroid function tests were within normal limits. The ultrasound neck showed an isthmic nodule with internal vascularity. Thyroid Scintigraphy images of this patient are shown in the picture: TcO4 thyroid images showing cold nodule in isthmus and Tc Sestamibi image showing significant MIBI uptake in initial image with partial retention in delayed image raising the possibility of a malignant nodule. Patient underwent total thyroidectomy and biopsy was reported as follicular variant of papillary carcinoma. This case highlights the potential use of sestamibi scan in improving the detection of malignancy more accurately.



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pkp9918@rediffmail.com,
prasanta@sgpgi.ac.in

Address For Correspondence :

Dr. Prasanta Kumar Pradhan
Associate Professor,
Dept. of Nuclear Medicine,
Sanjay Gandhi Post Graduate Institute of Medical Sciences (SGPGIMS),
Lucknow, India. 226014.
Ph : 00-91-522-2668700-2617(O)
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Thyroid Watch

Compiled by A Ghosh

1. **Prevalence of thyroid dysfunction in Turner's syndrome**: The prevalence of hyperthyroidism, hypothyroidism and elevated auto antibodies were 2.5%,24% and 42% respectively in 84 girls with Turner's syndrome (0.5 to 19 yrs) who were followed up for a mean period of 8.4 +/-4.4 yrs. Elevated antithyroid antibodies were present in 65% of hypothyroid cases. Thyroid dysfunction was observed mainly after the age of 8 years Hence thyroid function should be evaluated yearly in girls with Turner's syndrome past the age of 8 years and more so in those with positive antibodies. (Thyroid 2005;15(9):1061-6.)

2. **Type 1 diabetes with autoimmune thyroid dysfunction and arterial stiffness** : In a randomized control trial, 31 female type I diabetic patients (11 although euthyroid during study period, had concomitant auto immune thyroid disease) were assessed for arterial stiffness using applanation tonometry and pulse wave analysis .Results were compared to 24 healthy subjects . In all of them flow mediated dilatation and intimal medial thickness of carotids were measured . It was observed that women with type 1 diabetes had increased arterial stiffness which indicates a higher risk of macroangiopathy. Concomitant autoimmune thyroid disease seems to aggravate arterial compliance in these patients, a finding that merits further evaluation . (Endocrinology Invest 2005;25(7):616-22.)

3. **Thyroid hormone dysregulation in intrauterine growth retardation associated with maternal malnutrition and/ or anemia** : In a prospective study, the effects of maternal malnutrition and / or anemia on thyroid hormone profile of neonates and maternal blood were analyzed. Higher levels of cord blood T_4 and corresponding lower T_3 and rT_3 were observed in the neonates born to anemic and malnourished mothers and there was decrease in cord blood T_3 levels in small for gestational age babies . The study concluded with the speculation that these alteration in the thyroid function result in beneficial adaptations to the hostile intrauterine environment in malnutrition related growth retardation and anemia . (Hormone Metabolism Res 2005;10:633-40.)

4. **Reverse transcriptase (RT) inhibitors down-regulate cell proliferation and retain thyrotrophin signaling and iodine uptake in human thyroid anaplastic carcinoma** : In this in vitro study on cultured anaplastic thyroid carcinoma cells RT inhibitors (nevirapine and efaverenz) reversibly inhibited cell proliferation without triggering cell death in

cultured cell illness and caused cellular differentiation with up regulation of TSH receptor, thyroglobulin, TPO and Na/I symporter genes. RT inhibitors also reestablished the ability to uptake iodine in response to TSH. Further clinical trials are needed to clarify the speculated role of RT inhibitors in restoring the sensitivity to radio metabolic therapy in anaplastic thyroid tumors. (J Clin Endocrnol Metab 2005;90(10):5663-71).

5. **Psychiatric disorders in Hashimoto disease and euthyroid goiter** : In a population based case control study, 19 euthyroid subjects with Hashimoto disease and 19 euthyroid subjects with goiter were compared with 2 matched control groups for occurrence of psychiatric disorders. Subjects with Hashimoto disease showed higher frequencies of life time depressive episode (OR-6.6), generalized anxiety disorders (OR-4.9) and social phobia (OR-20) while no differences were found between subjects with goiter and controls. (Clinical Pract Epidemiol Ment Health 2005;1(1):23.)

6. **Maternal hypothyroidism in early and late gestation and neonatal and obstetric out come:** In a retrospective study of 167 pregnancies, neonatal and obstetric outcome was studied in relation to the TSH level at first presentation and in the third trimester. Study concluded with the observation that thyroxine dose requirement increases during pregnancy; maternal hypothyroidism at presentation and in the third trimester increased the risk of low birth weight and likelihood of caesarean section. (Clinical Endocrinology 2005;63:560-5).

7. **Management of Graves' disease during pregnancy and role of fetal thyroid gland monitoring** : In a prospective randomized controlled trial, 72 pregnant women with Graves' disease and their fetuses were monitored monthly from 22 weeks of gestation (fetal thyroid size ,doppler signals and bone maturation were determined on ultrasonograms and thyroid function was evaluated at birth; Thyroid function and antithyroid drug dosage were monitored in the mothers). 11 fetuses were detected to have goiter by ultrasonography at 32 weeks. All of them had thyroid dysfunction and treatment showed significant improvement in peri-natal outcome with ten of them having normal or slightly altered thyroid function . This study proposed that ultra sound at 32 weeks (by an experienced ultrasonographer) has a sensitivity and specificity of 92 and 100% respectively for the diagnosis of clinically relevant fetal thyroid dysfunction in this patient group. (J Clin Endocrnol Metab 2005;90(11):6093-8.)

8. **Aggregation of high-normal TSH in hypertensive families :** The concordance of high normal TSH among hypertensive, multiple sibling families was greater than expected by chance (p=0.009) in 333 euthyroid hypertensive subjects including 229 members of multiple sibling families and 31 normotensive subjects with family h/o hypertension. Healthy normotensives with a family h/o hypertension had significantly higher TSH values than those with a negative family h/o hypertension. The study concluded with the observation that there was familial aggregation of a high normal TSH level in hypertensive families, and that a family history of hypertension influenced TSH levels in healthy subjects. (J Clin Endocrnol Metab 2005;90(11):5985–90.)

9. **Cycloxygenase 2 inhibitors reverse chemoresistence pheotype in medullary thyroid Ca (MTC) by a permeability Glycoprotein(p-gP) –mediated mechanism :**An in vitro study demonstrated that primary culture of MTC cells expresses both, the p-gP (which is coded by MDR-1gene and functions as a membrane efflux pump conferring resistance to

many chemo therapeutic drugs in cancer cells) and the COX 2 (which regulates MDR-1 expression). The use of COX-2 inhibitors was shown to sensitize cytotoxic effect of doxorubicin in primary cultures of MTC by reducing P-gP expression and function . (J Clin Endocrnol Metab 2005;90(10): 5754-60.)

10. **Single recombinant human thyrotrophin(rhTSH) stimulated serum thyroglobulin(Tg) measurement predicts Differentiated Thyroid Carcinoma(DTC) metastasis after 3 to 5 years:** In a prospective follow up study of 107 DTC patients, who were stratified according to their initial rhTSH stimulated Tg levels, as group 1 with Tg < 0.5 (n-68), group II with Tg of 0.6-2 (n-19) and group III with Tg >2 ng/ml (n-20). They were followed up for 0.9-5 years. Persistent tumor was identified in 1.6%, 5.5% and 80% of subjects in group I, II and III respectively . Study concluded with the observation that a single rhTSH stimulated Tg >2 ng/ml predicts persistent tumor and repeated TSH stimulated studies are appropriate for patients at high risk of tumor recurrence (Tg > 1ng/ml). A single rhTSH stimulated Tg <0.5ng/ml without Tg antibody has 98% likelihood of identifying patients free of tumor. (J Clin Endocrnol Metab 2005;90(9):5047-57).

Thyroid Research and Practice

Guidelines for manuscript submission

Thyroid Research and Practice will publish original articles, case reports, pictorial images and reviews relevant to thyroidology. Letters to the editor will also be published. The manuscripts will be considered for peer review only if neither the article nor any part of it has been published or submitted elsewhere prior to submission to the journal. This restriction does not apply to abstracts published with scientific meetings. Submit three copies with original figures and a copy on disk. Use standard-sized paper and double -space throughout. Address all submissions to : The Editor, Thyroid Research and Practice, Indian Thyroid Society, Regd Office: Amrita Institute of Medical Sciences, Elamakkara P.O., Cochin - 682 026, Kerala, India.

The Covering Letter

A covering letter should be submitted. This must be signed by all authors and should indicate the corresponding author (with the address, phone number, fax number and e-mail address). The letter should state that the final manuscript has been approved by all authors, that the study has not been published (or submitted elsewhere) so far and also that the authors accept total responsibility for the study. If there is any financial grant that requires acknowledgment, it is to be documented on this page.

Other guidelines:

- The abstract should be less than 250 words and need not be structured
- 3 to 10 keywords may be provided
- Legends for figures should be triple-spaced on a sepa` rate sheet.
- Original articles must follow the sequence : Introduction, Methods, Results and Discussion.
- The Thyroidology Images section must have a title and a short description of less than 80 words.
- Case reports must have an abstract, introduction, description of the case and a short discussion.

References

References must be numbered in the order that they are cited. The submitters should list all the authors when they are six or less; if there are seven or more authors, then list the first three, then "et al" The following are some examples:

1. Mondal A, Patra DK. Efficacy of fine needle aspiration cytology in the diagnosis of tuberculosis of the thyroid gland: a study of 18 cases. J Laryngol Otol 1995; 109: 36-8
2. Pyorala K, Pedersen TR, Kjekshus J, Faergeman O, Olsson AG, Thorgeirsson G. Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease. A subgroup analysis of the Scandinavian Simvastatin Survival Study (4S) Diabetes Care 1997; 20:614-20.
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4. Boyages SC. Primary pediatric hypothyroidism and endemic cretinism. In: Bardin CW, ed. Current therpy in endocrinology and metabolism. 5th Ed. S t. Louis: Mosby, 1994: 94-98

Units of Measurement

Authors should express all measurements in conventional units and it will be appreciated if Systéme International (SI) units are provided in parentheses. Figures and tables are to use only conventional units.

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1. Data on file (KEM Hospital, Mumbai)

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