



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.

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

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Editorial

Not just next to the thyroid! Searching for the elusive parathyroid adenoma

AG Unnikrishnan*, T Babu**, A Premkumar*, RV Jayakumar*, H Kumar*

*“ The parathyroid gland seldom remains in one place”
-Wang’1977*

Diagnosing hyperparathyroidism

Worldwide, primary hyperparathyroidism (PHPT) is the commonest cause of hypercalcemia. Commonly, 85% of cases are secondary to a solitary parathyroid adenoma. About 15% result from hyperplasia or multiple adenomas. Less than 1% are caused by parathyroid carcinoma. While most of these adenomas are in the neck, sometimes the parathyroid adenoma may exist outside their expected sites, the so-called “ectopic” glands.

A high parathormone level confirms the diagnosis of PHPT, and surgery is the only effective therapy. While surgical neck exploration is the best method to detect these glands, increasing evidence suggests that pre-operative localization is crucial. This is because early localization can enable minimally invasive surgery (MIS), decrease operative time, reduce length of hospital stay and decrease the incidence of postoperative hypoparathyroidism. But the most important argument for preoperative localization is that it can identify ectopic parathyroid glands and thus decrease the need for re-exploration.

Embryology

The “ectopicity” of parathyroid glands is linked to their migration in the embryonic period itself. . The two *superior* parathyroid glands arise from the 4th branchial pouch. They are usually constant in their locale and are found just posterior to the thyroid gland. When ectopic, they may be encountered in the superior or posterior mediastinum. The two *inferior* parathyroid glands arise from the 3rd branchial pouch. They are located within 1-2 cm from where the inferior thyroid artery enters the thyroid gland. They are slightly more nomadic and ectopic sites include: the tracheoesophageal sulcus, the paratracheal fat, or the thymus (another third pouch derivative). In general, when ectopic, they seem to prefer the *anterior* superior mediastinum. Another common ectopic site is within the thyroid gland itself (intrathyroidal). The anterosuperior

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mediastinum, in or around the thymus, is probably the most common ectopic site for parathyroid tissue.¹

Methods of Localization

The commonly used localization techniques are detailed below and in table 1.

Table 1. Localization techniques for parathyroid adenoma

Ultrasound
CT scan
Fine needle aspiration (FNA)
MRI,
Sestamibi scan
SPECT-MIBI
Angiography /selective venous sampling,
Surgery
Intraoperative PTH
Radio-guided intraoperative techniques

Ultrasound: Ultrasonography is approximately 50-75% sensitive in identifying adenomas in the neck. It has low sensitivity in identifying ectopic lesions. Adenomas are well-defined hypoechoic lesions, sometimes with potential cystic or necrotic areas. Ultrasonography also helps diagnose concomitant thyroid disease, present in about 40% of patients with parathyroid disease.

CT Scan: A CT scan before and after contrast is ideal. Before administration of contrast material, parathyroid adenomas have attenuation that is equal to muscle. Parathyroid adenomas are usually vascular, but contrast enhancement is quite variable. However an enhancing soft-tissue mass near the expected location of the parathyroid glands is highly suggestive of an adenoma. The reported sensitivity ranges from 40 to 90%.

FNA: If a suspicious nodule is identified, FNA can identify parathyroid lesion. This is very useful if there has been a failed neck exploration, and to ensure that the second surgery will accurately remove the parathyroid lesion. This is important in elderly patients or subjects with co-morbid illnesses, in order to minimize the time spent under anesthesia.

MRI: Usually, normal parathyroid glands are not identified on MRI. On T1-weighted images, adenomas are low-signal masses. On T2-weighted images, intermediate or high signal intensity is seen. Gadolinium enhancement can enhance the adenoma. MRI is quite useful in detecting ectopic glands, and the sensitivity is about 88-96%.^{2,3}

^{99m}Tc Sestamibi Scan: Arguably, this isotope scan is the best diagnostic test. On sestamibi injection, initially, both thyroid and parathyroid glands take the tracer. By about 2-4 hours, the thyroid gland washes out the tracer, and the parathyroid adenoma or carcinoma, which still retains it, “lights up”. A single film and a single injection are adequate, unlike the now out-of-fashion thallium-technetium subtraction scan. When combined with 3-D SPECT scanning a 3 dimensional view of the tumor is obtained. ^{99m}Tc tetrofosmin is another useful test. The reported sensitivity of the Sestamibi scan is about 90-100%.

Angiography / venous sampling: Angiograms localize parathyroid tumors in about 60% of cases. They may additionally permit angioablation too. The inferior thyroid arteries usually supply the parathyroid glands, and when the dye is injected into this vessel, a characteristic blush (also called a stain) appears, and lesion is usually round or oval with smooth margins. Rarely, the superior thyroid artery or the thyroidea ima vessel supplies the parathyroid gland. If the small vein draining the gland is also cannulated after the arteriogram gives the “road map”, then samples are drawn for PTH estimation. A simultaneous peripheral vein sample too is obtained. A parathyroid: peripheral ratio > 2 is considered significant.

Surgery, intraoperative PTH and the hand-held gamma probe: It has been quipped that the best method to localize the parathyroid adenoma is to localize a good surgeon. The sensitivity of surgery is more than 98% when the surgeon is experienced in parathyroidectomy. Recently, several diagnostic methods have been used to further improve surgical outcome, and we describe our institution’s experience with these methods. The first among them is intraoperative PTH estimation or “Turbo PTH assay”. Before surgery, baseline samples for PTH are taken. At the time of neck exploration,

once the adenoma is removed, then we take venous samples at the time of adenoma removal (2 minute) and at 20 minutes. Once the PTH has fallen by 50% of the baseline value at 2 or 20 minutes, the surgeon abandons his search for another adenoma. If the fall in PTH has been suboptimal, then exploration is continued till the other lesions are identified and removed. This protocol can successfully diagnose double adenomas or even multiple lesions. We also recount our experience with the use of the hand-held gamma probe for aiding surgical localization. ^{99m}Tc sestamibi is injected before surgery. A hand-held gamma probe is used to detect tracer activity. This guides the incision and localization of abnormal gland. This method is increasingly being used to improve surgical outcomes. These techniques help the surgeon to continue or terminate his search, gives instant feedback regarding the progress of surgery, allows the surgeon to take the minimally invasive approach and also reduce surgical complications.

The Future: Robots, Fusion and Cinacalcet

In future, several innovations promise to improvise on existing techniques: Recently, the use of robot-assisted-parathyroid-surgery has been reported.⁴ A second innovation has been that the advantages of CT and Sestamibi have been synergized to produce fusion images with the help of overlaying radiographic markers and sophisticated software. The fusion provided better resolution of enlarged parathyroid tumors and adjacent structures.⁵ Finally, with the advent of calcimimetic agents like cinacalcet, the issue of localization may become more controversial. These molecules help the parathyroid gland in recognizing the high calcium levels and assist the gland in switching down the level of PTH secretion.^{6,7} It is hoped that these exciting innovations will usher in a new era in the management of primary hyperparathyroidism.

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Review Article

Management of maternal hypothyroidism : a practical perspective

AG Unnikrishnan

Abstract

The occurrence of Hypothyroidism in pregnancy is linked to adverse effects on mother and the fetus. Recent research has indicated that in the first half of pregnancy, an adequate thyroid hormone level could play an important role in fetal brain development. Clinical signs of hypothyroidism in pregnancy are not very specific and sensitive. Therefore, serum TSH estimation is the best way to make a diagnosis. Hypothyroidism in pregnancy, whether overt or subclinical, requires therapy with levothyroxine. Frequent monitoring and precise dose titration are required. The aim of therapy is to achieve a TSH value that is < 2.5 mu/L, and this is important to ensure a successful pregnancy outcome.

Key words: Graves' ophthalmopathy, clinical activity score, immunosuppression.

Introduction

Hypothyroidism during pregnancy poses a challenge to the treating clinician. The diagnosis is made by a TSH that is greater than normal, and during pregnancy, this situation deserves therapy. Research over the years has shown that maternal thyroid hormones are very important in pregnancy.¹⁻³ Importantly, emerging data seems to suggest that thyroid hormones are important for fetal brain development, especially during early pregnancy.⁴ This article will focus on the clinical approach to hypothyroidism in a pregnant woman.

Pregnancy-related alterations in thyroid physiology

Pregnancy can cause several physiological changes in thyroid function tests (Table 1).⁵⁻⁹ The requirement for thyroid hormones is increased during pregnancy, and this is achieved by an increased thyroid gland function. The thyroid gland of subjects with pre-existing hypothyroidism lacks the functional reserve to increase thyroxine secretion appropriately. This results in a 25-47% increase in levothyroxine dose requirement during pregnancy.⁵

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Lack of adequate iodine intake is another factor that can compromise thyroid function in pregnancy, especially in iodine-deficient zones.^{6,7} hCG too is an important factor confounding thyroid function tests. HCG has a structure that is similar to TSH- thus hCG too can stimulate the thyroid gland. This causes transient suppression of TSH in the first trimester.⁸ Finally, the estrogenic milieu of pregnancy results in increased sialic acid content of thyroid binding globulin (TBG); this reduces the clearance of TBG and prolongs its circulation time.⁹ This increase in TBG (which binds to thyroid hormones) can result in a falsely high thyroid hormone (especially T4) levels during pregnancy. However adaptation mechanisms ensure that the free or active thyroid hormone levels are kept normal. Though these changes affect both the

thyroid hormones (T3 and T4), T4 is the more appropriate hormone to measure, and it has been suggested that free T4 hormones be measured in pregnancy. In case total T4 is being used as a measuring tool, recent reports suggest that a different cut-off be used. It has been reported that the normal upper limit of total T4 level is 1.5 times the upper limit in non-pregnant adults. Postpartum thyroiditis is an important pregnancy-related thyroid disease. Autoimmune thyroid disorders remit during pregnancy as a part of the immunosuppressive effects of pregnancy. Classically, there is a post-partum period of exacerbation. A key finding associated with thyroid autoimmunity is that patients who are euthyroid but positive for antibody have an increased rate of miscarriage.¹⁰ The reason for this is not well understood.

Table 1. Some physiological thyroid alterations in pregnancy

Phenomenon	Explanation
High thyroxine-binding globulin (TBG)	Increased serum estrogen
First trimester TSH suppression	hCG
Slight increase in FT4	hCG
Goiter in iodine deficient areas	Increased iodide clearance
Goiter in iodine sufficient areas	Increased demand
Increased T4 and T3 demand	High type III deiodinases
High total T4 and T3	Increase in TBG
Increased thyroglobulin	Increased demand for thyroid hormones

Hypothyroidism during pregnancy: clinical importance

Hypothyroidism, as defined by a raised TSH level, affects 2.5% of all pregnancies.¹¹ Thus, about 40 patients need to be screened to detect one case. In iodine-sufficient areas, the most common cause is Hashimoto's thyroiditis. The issue of universal screening during pregnancy for this common, serious and easily treatable disease definitely merits consideration, but is a hotly debated controversy.

The diagnosis of maternal hypothyroidism is important because of its implications on both maternal and fetal outcomes (Table 2).^{2,12} This is even true with subclinical hypothyroidism.¹³ In addition, it is well known that untreated hypothyroidism can cause infertility.¹⁴

Emerging evidence in the last decade has linked thyroid hormones with fetal brain development. Classic studies on neurological cretinism had earlier shown that iodine deficiency caused fetal brain damage.¹⁵ This occurs presumably by reducing thyroid hormone synthesis, as iodine is an integral component of both T3 and T4. However, in addition to iodine deficiency, any cause of maternal hypothyroidism in early pregnancy can cause fetal brain damage.

Thyroid gland develops in the fetus only after 3 weeks. This thyroid gland can trap iodine and synthesize thyroid hormones only after about 3 months. Till this time, the mother gives thyroid hormones to her fetus through placental diffusion. Even after 3 months, maternal T4 transfer continues.¹² In order to know whether this transfer was significant, Vulsma et al studied 25 neonates with complete inability to produce thyroid

hormones.¹⁶ T4 levels in the cord serum of affected neonates ranged from 35 to 70 nmol/liter. The authors concluded that this level was purely acquired from maternal thyroxine (T4) transfer, and that this indicated substantial maternal-fetal thyroxine transfer during the first trimester. Do these transferred hormones serve any important function? In animal studies, thyroid hormones regulate neuronal proliferation, migration of neurons, synapse formation and myelination.¹⁷⁻¹⁹ It has been hypothesized that T4 gets converted to triiodothyronine (T3) in the cerebral cortex, which binds to specific nuclear receptor isoforms to carry out these functions. Hypothyroidism as a result of low maternal T4 may be overt or mild, presenting with very subtle neurological defects, like learning disabilities or a low intelligence quotient.¹⁷⁻¹⁹ However, the evidence linking hypothyroidism with poor obstetrical outcome is much stronger than that linking it to neurological outcomes. To summarize, published evidence suggests that maternal hypothyroidism is common, and that it is of crucial significance during both early and late pregnancy.

Table 2. Adverse outcomes associated with maternal hypothyroidism

Maternal disorders
Abortion
Gestational hypertension
Increased use of cesarean section
Anemia
Placental abruption
Preterm labor
Postpartum hemorrhage
Fetal disorders
Premature birth
Fetal and perinatal death
Disorders of brain development
Low IQ scores Fetal respiratory distress
Low birth weight
Cretinism

Diagnosing maternal hypothyroidism

It is difficult to detect hypothyroidism during pregnancy based on symptoms and signs alone. Thus, the diagnosis is made by serum TSH estimation. Trimester-specific normative TSH data are important in this regard, but need to be validated.²⁰ A TSH value that is more than the upper limit of normal (i.e. >4mU/L) should alert the clinician to the diagnosis. Recent studies have suggested that either a total or free T4 must also be simultaneously tested during screening.²¹ This is because a low T4, even with a normal TSH, is now considered abnormal (especially in iodine deficient zones), and this deserves therapy. Thus, the focus seems to be shifting towards maternal hypothyroxinemia rather than hypothyroidism.²¹

In general, free T4 estimation is important in pregnancy. However, the total T4 is increasingly being used nowadays, given fallibilities in the free T4 assay. Normal levels of total T4 in pregnancy can be decided by multiplying non-pregnant levels by a factor of 1.5 for pregnant women.⁵ Antithyroid antibody testing is not mandatory, but can be useful because it identifies an underlying autoimmune basis. Also, high antithyroid antibody titers are associated with infertility and pregnancy losses.²²

Treatment

Levothyroxine (LT4) is the treatment of choice. In subjects with florid, overt hypothyroidism, the dose required is 2 ug/kg/day.⁵ This higher dose is important to cover for higher thyroxine demand during pregnancy. In subjects with subclinical hypothyroidism and in subjects with a TSH < 10 mU/L, the starting dose of LT4 is usually 50-100ug/ day.

Considerations are different in subjects with “pre-gestational” hypothyroidism i.e. in subjects who have become pregnant while already taking LT4 for hypothyroidism. These subjects require a 25-47% increase in dosage. This excess need is because of excess TBG, increased distribution of T4 as well as the placental transport of thyroid hormones. It has been recommended that when a hypothyroid woman taking LT4 becomes pregnant, the dose should be increased by about 25-50 ug as soon as pregnancy is diagnosed.²³ Usually, the dosage required is stable and plateaus beyond the 20th week. Thus, after this time, very frequent monitoring is not needed.²³

²⁴ Women taking iron or calcium tablets should not take them simultaneously with LT4. These tablets may be taken about 4 hours after taking LT4. Iodine intake is important in pregnancy.²⁵

Monitoring and targets

In the first half of pregnancy, it is best to monitor with free T4 and TSH every 4 weeks. But later on, the monitoring may be done every 6 weeks. The target TSH level in pregnancy is <2.5 mU/L.⁵ In subclinical hypothyroidism, the dose may be increased by about 50ug at a time. However, in cases where the TSH is high (>10 mU/L), the dosage may need to be increased by 50-75 ug at a time. Where TSH is > 20 mU/L the dose may need to be increased by 75-100 ug at a time. Post-delivery, the dose must be reduced to the pre-pregnancy dosage. Thyroid functions may be re-checked when 6 weeks have elapsed following delivery.

Isolated anti-thyroid antibody positivity: an enigma

Pregnancy loss has been linked to thyroid autoimmunity.²⁶ The reasons are hypothetical: firstly, antithyroid antibodies may only be a marker of generalized autoimmunity, which could explain the high occurrence of miscarriages.²² It is also possible that anti-TPO (anti-thyroid peroxidase) antibodies, a marker of autoimmune thyroid disease (AITD) could pick out groups of subjects with subtle damage to the thyroid gland. These subjects might be at risk of developing hypothyroidism because the thyroid gland that is damaged via autoimmune mechanisms is unable to adjust to the physiological loads that are imposed on it during pregnancy.²² The third hypothesis suggests that both anti-TPO positivity as well as miscarriages are common in older women: thus the link between thyroid autoimmunity and pregnancy loss is a statistical aberration that is due to the confounding effect of age.²² None of these hypotheses have been proved or disproved, despite several studies on this issue. In a recent study, the authors reported that LT4 therapy in euthyroid TPO+ve pregnancies could improve miscarriage rate by 75% and premature deliveries by 69%.²⁷ This study implies, but cannot conclude with certainty, that the judicious use of levothyroxine could improve outcomes, especially in pregnant,

anti-TPO positive subjects with a high-normal TSH. Future studies looking into this emerging area are needed before clinical recommendations can be made.

Summary and recommendations

Hypothyroidism during pregnancy is common, and can have serious consequences on obstetrical and fetal outcomes. Diagnosis is based on serum TSH estimation. Levothyroxine is the therapy of choice. Frequent monitoring every 4-6 weeks and dose titration are important. Indeed, a recent guideline suggests that thyroid functions (T4 and TSH) should be normalized “as rapidly as possible” when hypothyroidism complicates pregnancy.²⁸ These guidelines recommend target TSH values that are < 2.5 mU/L in the first trimester, and < 3 mu/L in the 2nd and 3rd trimesters.²⁸ When T4 measurements are also used, the guidelines suggest that total T4 could be a very reliable test, and advise caution while interpreting free T4 measurements.²⁸ It seems likely that the focused treatment of hypothyroidism during pregnancy will become more important in the years to come.

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Original Article

Prevalence of musculoskeletal manifestations in thyroid disease

MG Pillai *, V Kumaravel**, B Nisha ***, C Hareesh ***, AG Unnikrishnan ***, V Nair***, RV Jayakumar ***, H Kumar***

Abstract

Musculoskeletal symptoms and signs are common and may be the only presenting complaint in hypothyroidism. There are no published studies on this aspect of thyroid disease in our population

Aim: To assess the prevalence of various musculoskeletal manifestations of hypothyroidism.

Methods: Eighty eight consecutive patients with hypothyroidism and no other underlying chronic diseases were evaluated with questionnaire on musculoskeletal symptoms and physical examination for any abnormality in musculoskeletal system

Results: 76.1 % had some symptom with our questionnaire and 45.5% had some physical abnormality. 77.8 % of patients with overt hypothyroidism were symptomatic whereas 72% patients with sub clinical hypothyroidism were symptomatic. 49.2% of patients with overt hypothyroidism had some abnormality in physical examination, the corresponding figure was 36% for sub clinical hypothyroidism.

Conclusion : Signs and symptoms of musculoskeletal involvement are very common in hypothyroidism.

Key Words : Hypothyroidism, myopathy, effusion, musculo skeletal.

Introduction

Musculoskeletal symptoms and signs are common and may be the only presenting complaint in hypothyroidism, but are often not considered among the classic clinical features of this common illness.^{1,2} Hypothyroid patients, often complain of articular and muscular pains and even may present with joint effusions involving knees or small joints. Myopathy suggesting polymyalgia rheumatica, nerve entrapment and tenosynovitis are diagnoses that should be considered in these patients. A variety of musculoskeletal symptoms and signs have been reported in patients with thyroid diseases

Previous studies have attributed the high prevalence of musculoskeletal involvement in Hashimoto's disease to the autoimmune nature of this disease.³ To the best of our

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knowledge, there are no published studies on this aspect of thyroid disease in our population.

Our aim is to assess the prevalence of various musculoskeletal manifestations of hypothyroidism in our patients and to assess whether they correlate with markers of thyroid autoimmunity. We also looked at whether these were a feature of sub clinical hypothyroidism as well and whether thyroid replacement therapy lead to improvement in symptoms.

Methods

Eighty eight consecutive patients with hypothyroidism who attended the department of Endocrinology & Diabetes at Amrita Institute of medical sciences were included in our study. None of the patients had chronic diseases like Diabetes mellites, connective tissue disease, hepatic dysfunction, renal disease or any other major illnesses. We used a standardized symptom questionnaire administered by the physician and physical examination protocol performed by a trained physiotherapist, based on a previous study, to assess the prevalence of musculoskeletal deformity in these patients.⁴ The questionnaire evaluated presence of symptoms such as parasthesia or dysesthesia in hands and feet, proximal or distal

Figure 1. Shows Dupuytren’s contracture in a hypothyroid patient



muscle weakness, easy fatigability with daily activities, restriction of joint mobility and presence of musculoskeletal pain including morning stiffness.

Physical examination focused on abnormality of range of movements, presence of soft tissue swelling or effusion of joints, Tinel’s sign, Phalen’s sign, signs of shoulder adhesive capsulitis, limited joint mobility in the form of Prayer sign, Dupuytren’s contracture, trigger finger and signs of fibromyalgia. Investigations including Thyroid stimulating hormone(TSH), free T4, anti thyroid peroxidase and / FNAC of thyroid, erythrocyte sedimentation ratio(ESR), Serum

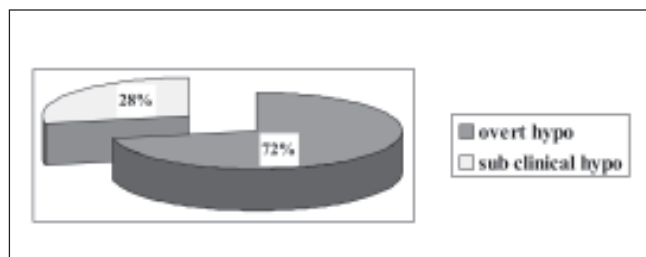
Figure 2. Shows prayer sign in a hypothyroid patient.



Calcium, Phosphorus, alkaline phosphatase, creatine phospho kinase(CPK) and lactate dehydrogenase(LDH) were done in all the patients. All statistical analysis was done using SPSS.

Results

Pie chart showing distribution of cases



Out of the 88 patients, 83 were females. Mean age was 40.05 +/-11.86 years. Of the 88 patients, 63 patients had overt hypothyroidism and 25 had sub clinical hypothyroidism. Forty six patients had Hashimoto’s disease as established by anti TPO positivity or FNAC. The prevalence of the commonly detected musculoskeletal abnormalities in our patients are shown in tables 1 and 2. There was no significant difference between patients with Hashimoto’s disease and the other groups regarding the prevalence of these features. Besides, a significant proportion of patients with sub clinical hypothyroidism also had musculoskeletal abnormalities.

Table 1. Prevalence of musculoskeletal symptoms in hypothyroid patients.

Symptoms	Hashimoto	Non Hashimoto	Not known	Overt hypothyroid	Sub clinical hypothyroid
Sensory	17/46 (36.9%)	8/22 (36.4%)	5/20 (25%)	24/63 (38.1%)	6/25 (24%)
Muscular	15/46 (32.6%)	10/22 (45.5%)	9/20 (45%)	26/63 (41.3%)	8/25 (32%)
Proximal muscle weakness	15/46 (32.6%)	12/22 (54.5%)	8/20 (40%)	27/63 (42.9%)	8/25 (32%)
Musculoskeletal pain	32/46 (69.6%)	16/22 (72.7%)	16/20 (80%)	47/63 (74.6%)	9/25 (36%)
Shoulder pain	17/46 (36.9%)	7/22 (31.8%)	6/20 (30%)	21/63 (33.3%)	9/25 (36%)

77.8 % of patients with overt hypothyroidism were symptomatic whereas 72% patients with sub clinical hypothyroidism were symptomatic. 49.2% of patients with overt hypothyroidism had some abnormality in physical examination, the corresponding figure was 36% for sub clinical hypothyroidism. As a whole, 76.1 % had some symptom with our questionnaire and 45.5% had some physical abnormality.

Adhesive capsulitis of the shoulder was present in 6 patients. Tinel's sign was positive in 11 patients and Phalen's test in 4 patients. Prayer sign was present in 17 patients. Dupuytren's contracture involving left little finger was present in one patient. Enzymes were normal in 87/88 patients. None of the patients fulfilled the criteria for fibromyalgia.

Follow up data was available for only 12 of these patients at the time of writing this paper. In 11 of these 12 patients, there

Table 2. Prevalence of musculoskeletal abnormalities on examination in hypothyroid patients.

Examination findings	Hashimoto's	Non Hashimoto's	Not known	Overt hypothyroid	Sub clinical hypothyroid
Delayed relaxation of DTR	2/46 (4.4%)	1/22 (4.5%)	1/20 (5%)	3/63 (5%)	0/25
Abnorm range of movements	12/46 (26.1%)	11/22 (50%)	4/20 (20%)	21/63 (33.35)	6/25 (24%)
Joint effusion	0	2/22 (9.1%)	1/20 (5%)	2/63 (3.2%)	1/25 (4%)
Swelling of joints	5/46 (10.9%)	4/22 (18.2%)	2/20 (10%)	6/63 (9.5%)	3/25 (12%)
Tinel sign	5/46 (10.9%)	4/22 (18.2%)	2/20 (10%)	7/63 (11.1%)	4/25 (16%)
Phalen sign	3/46 (6.5%)	1/22 (4.5%)	0	3/63 (5%)	1/25 (4%)
Shoulder adhesive capsulitis	2/46 (4.4%)	1/22 (4.5%)	1/20 (5%)	3/63 (5%)	0/25
Dupuytren's	12/46 (26.1%)	11/22 (50%)	4/20 (20%)	21/63 (33.35)	6/25 (24%)
Prayer sign	0	2/22 (9.1%)	1/20 (5%)	2/63 (3.2%)	1/25 (4%)

was at least 75% relief of symptoms with thyroid hormone replacement therapy.

Discussion

Hypothyroidism is frequently accompanied by musculoskeletal manifestations ranging from myalgias and arthralgias to true myopathy and arthritis. Most cases of arthropathic changes in adult-recognized hypothyroidism involved the knees and hands, while the hip and the epiphysis of the femoral head appear more commonly involved in children. Thyroid hormones have known effects at the cellular level on proliferation and differentiation of bone and cartilage. The hypothyroid state appears to induce abnormalities in these tissues, which result in such clinical manifestations as epiphyseal dysgenesis, aseptic necrosis, possibly crystal-induced arthritis, and an arthropathy characterized by highly viscous noninflammatory joint effusions primarily affecting the knees, wrists, and hands. Neuropathic and myopathic symptoms accompanying hypothyroidism may manifest as joint region abnormalities when in fact there is no underlying arthropathy.^{4,5}

Adhesive capsulitis, also known as frozen shoulder, is a regional skeletal problem reported in association with thyroid disorders, in addition to other diseases such as diabetes mellitus, coronary artery disease, cerebrovascular events, pulmonary disorders and epilepsy. The prevalence of primary idiopathic AC in the general population has been reported as 2–3%.⁷ Deposition of hyaluronic acid and other mucoproteins is thought to cause the arthritis, myopathy, and carpal tunnel syndrome of hypothyroidism.

Muscle cramps and stiffness resembling those of fibromyalgia or polymyalgia rheumatica, or frank myopathy and high levels of creatine kinase, are often accompanied by arthritis. As many as one third of persons with hypothyroidism have painful, noninflammatory hyperviscous joint effusions in knees, wrists, and small joints of the hands that often disappear with replacement of thyroid hormones.⁶

Symptoms related to musculoskeletal system were common in our patients with hypothyroidism. 76.1 % of our patients had some sort of musculoskeletal symptom. But myalgia as

the sole presenting complaint was seen in only one patient. 45.5 % of our patients had some abnormality in musculoskeletal examination. In a previous study, in patients with various thyroid disorders, the prevalence of adhesive capsulitis was 10.9% and that of limited joint mobility was 4.4%.⁴ whereas in our study, the prevalence of adhesive capsulitis was 6.8% and that of limited joint mobility was 17.1%.⁷

In population based studies, limited joint mobility affects up to 5%, Whereas Dupuytren's contracture had an estimated prevalence of 19.2% in men and 4.4% in women.⁸ In our study limited joint mobility was seen in 33.5% of overt hypothyroidism and in 24% of subclinical hypothyroidism and dupuytren's contracture was seen in 33.35% of cases.

In the study by Punzi et al, in patients with chronic lymphocytic thyroiditis, the number of joints affected had a direct correlation with anti TPO levels and TSH levels.³ This was not present in our study.⁹

Conclusions

Signs and symptoms of musculoskeletal involvement are very common in hypothyroidism. They are often present in sub clinical hypothyroidism also. In two patients in whom follow up data was available, they had good relief with levothyroxine treatment. There was no correlation of the number of joints affected with anti TPO levels or TSH levels as reported in previous studies.

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Case Report

Uncommon presentation of primary hypothyroidism

A Mythili *, K Venkateswarlu**

Abstract

The clinical presentation of hypothyroidism often masquerades several illnesses. Dyslipidemia is a common accompaniment of hypothyroidism and these patients are more prone for statin induced myopathy. Treatment with levothyroxine itself is sufficient to correct the dyslipidemia. We report a case of primary hypothyroidism that presented with hyperuricemia, intractable hyperlipidemia and developed myopathy with usage of lipid lowering agents.

Introduction

The clinical presentation of hypothyroidism often masquerades several illnesses and a high index of suspicion is necessary for diagnosis. A diagnosis missed is often delayed for many months.¹ We describe a case of primary hypothyroidism who presented with hyperuricemia, hyperlipidemia and developed myopathy on lipid lowering agents.

Case presentation

A 42 year male presented to his physician 3 years back with swelling of feet for which he was given symptomatic treatment. Later he had swelling and pain of right first metatarsophalangeal joint. His uric acid was found to be elevated (Serum Uric acid 8.2mg/dL (normal:3.4-7mg/dl) and was prescribed Allopurinol. Evaluation also revealed dyslipidemia –Total cholesterol (TC) 259mg/dL, LDL 172mg/dL, Triglycerides (TG) 235mg/dL and HDL of 40mg/dL. Initially he was started on 10mg of Atorvastatin and later increased to 20mg without any response. Subsequently, gemfibrozil 600mg and fenofibrate 300mg were added for management of hypercholesterolemia and hypertriglyceridemia. He developed severe myalgias after starting the combination of statin and fibrates and was hence discontinued. Evaluation after six months revealed uric acid of 7.2mg/dL and persistent dyslipidemia – TC 296mg/dL, LDL 193mg/dL, TG 227mg/dL and HDL 58mg/dl. He again developed severe painful muscle aches after restarting statins for 4 days, necessitating discontinuation. A creatine phosphokinase (CPK) done was markedly elevated (15030 U/L) and myalgia disappeared after stopping statins. On questioning, he admitted having puffiness of face. There was no history of

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hoarseness of voice, recent weight gain, lethargy or bowel disturbances. He had somnolence which he attributed to cetirizine. There was a positive family history of thyroid disease in mother.

His weight was 70 kg, height 168cm and BMI 25kg/m². There was no pallor. He had bilateral non pitting pedal edema, periorbital puffiness and supraclavicular fullness. His Pulse rate was 72/min, blood pressure was 130/100mm Hg. Skin was dry and slightly coarse. Hair and nails were normal. Thyroid was palpable, diffuse and soft in consistency. Neurological examination revealed normal motor power in limbs. There was a slight delay in relaxation of ankle jerk. Other systems examination were normal. Investigations (Table -1) revealed low T3 and T4 and elevated TSH, mild proteinuria and >100 fold elevation of CPK.

A diagnosis of primary hypothyroidism was established. Lipid lowering agents and allopurinol were discontinued. He was

started on levothyroxine 100µg/day. He became euthyroid over next 3 months and cholesterol, triglycerides, uric acid levels returned to normal. A CPK estimation done after 3 weeks of stopping lipid lowering agents was 175U/L and the patient's myalgia and joint pain subsided. At the end of one year while on levothyroxine, patient was euthyroid with normal uric acid and Lipid profile.

Discussion

The index case is an example of delayed diagnosis of hypothyroidism manifesting with arthritis secondary to hyperuricemia, hyperlipidemia and statin induced myopathy. In the adult, the onset of hypothyroidism is usually so insidious that the typical manifestations may take months or years to appear and go unnoticed. The gradual development of the hypothyroid state is due to slow progression both of thyroid hypofunction and consequent clinical manifestations after thyroid failure is complete. If the diagnosis is not considered during the first encounter with the patient, it may

Table 1. Laboratory values

Fasting plasma glucose (70-110mg/dL)	74 mg/dL
Post Prandial glucose (<140mg/dL)	132 mg/dL
Serum creatinine (<1.5mg/dL)	1.2 mg/dL
Serum Calcium (9-10.5mg/dL)	9.4 mg/dL
Serum Phosphorous (3-4.5mg/dL)	3 mg/dL
Serum Albumin (3.5-5.5g/dL)	4.2 g/dL
C Reactive Protein (0-0.6)	0.7
Rheumatoid factor	Negative
ESR (1-25mm/1 st hr)	10mm/1 st hr
Creatine Phosphokinase (60-400U/L)	15,030U/L

take another 6 months before it is recognised that the multiple, seemingly disparate complaints are in fact due to hypothyroidism¹.

The patient presented with monoarthritis of the great toe and hyperuricemia. Mild hyperuricemia can occur in

hypothyroidism due to delay in clearance of uric acid. In a group of 28 patients with hypothyroidism, 32% had hyperuricemia, as compared with 2% -10% in the general population and 7% of those hypothyroid patients had gout.² The hyperuricemia was attributed to decreased renal plasma

flow and impaired glomerular filtration. Thyroxine therapy resulted in normalization of serum uric acid in the present case as reported in literature. Mild proteinuria may occur in hypothyroidism as evident in this case. It is due to decreased reabsorption of albumin and it disappears with treatment.

Dyslipidemia is a common accompaniment of hypothyroidism. Previously unrecognized or undertreated hypothyroidism has been reported in as many as 10% of patients referred for diagnosis and therapy of hyperlipidemia.³ Our patient had elevated total cholesterol, LDL and triglycerides. The classical hyperlipidemia of hypothyroidism is an elevation of the plasma LDL, but this disorder can also be associated with high plasma triglycerides. Levels of HDL are usually unchanged. Lipid alterations in hypothyroidism are secondary to decreased lipoprotein lipase activity, decreased LDL receptor expression, and alterations in hepatic lipase activity.

The widely disseminated NCEP ATP III guidelines have resulted in an increased number of patients receiving lipid lowering drugs. The incidence of clinically significant myopathy with any statin therapy is very low (<0.5%). One of the risk factors for development of myopathy with statins is hypothyroidism. The present case had significant myopathy with a combination of atorvastatin, gemfibrozil and fenofibrate along with undiagnosed hypothyroidism.

Hypothyroidism, with an associated myopathy and high CK, apparently facilitates the appearance of the otherwise very rare statin or fibrate-induced myopathy. As observed in this case, and in previous reports covert or undertreated hypothyroidism may be unearthed by fibrate or statin-induced myopathy.⁵ As in our case, lipid lowering drugs usually fail to optimally ameliorate hyperlipidemia in the face of untreated or undertreated hypothyroidism.

Moreover, the hyperlipidemia which accompanies hypothyroidism frequently improves or resolves with treatment of the hypothyroidism alone. The $t_{1/2}$ of atorvastatin is 14-20 hrs which may be prolonged in hypothyroidism. Mechanism of statin induced myopathy appears to be related to serum levels of the active molecules

that inhibit HMGCoA reductase. Addition of gemfibrozil also competitively inhibits statin glucuronidation and increases statin concentration.

The most common laboratory abnormality indicative of muscle dysfunction in hypothyroidism is a high serum creatine kinase (CK) concentration. However CPK levels also are high in as many as 70-90% of hypothyroid patients in whom there is no clinical evidence of muscle involvement. An occasional patient can have strikingly high serum CK concentration, more than 100 times the normal.⁶ The severity of symptoms associated with these markedly high values varies from no symptoms to substantial muscle weakness, muscle cramps and myalgia. The mechanism of high CK includes muscle fibre degeneration, altered muscle energy metabolism and decreased clearance of CK from the circulation. Our patient had >100 fold elevation of CK and levels returned to normal after statin was stopped.

A high index of suspicion is required to diagnose hypothyroidism. A measurement of TSH and T4 should be a part of work up of hyperlipidemia. Treatment of hypothyroidism alone is enough to correct hyperlipidemia. Failure to identify hypothyroidism and administration of lipid lowering drugs may precipitate iatrogenic myopathy.

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Thyroid Images

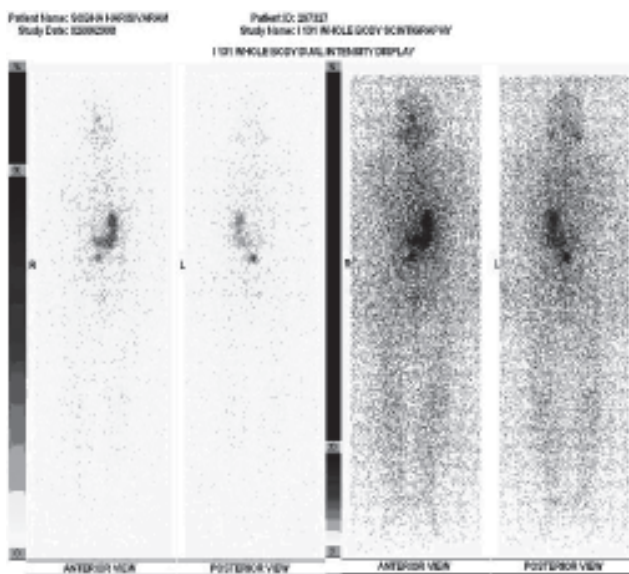
Compiled by
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A 45 year old female patient presented with complaints of radiating low back pain for 3 years in 2003. She was evaluated in an outside hospital and was found to have a mass lesion in L4 vertebra. In 2003 an open biopsy of L4 vertebra was done and was reported as Plasmacytoma which was treated with Radiotherapy. Since the pain was not decreasing, posterior open reduction & internal fixation with laminectomy of L4 vertebra was done in our institute. The resected tissue was reported as metastatic follicular carcinoma thyroid. She underwent a total thyroidectomy in another hospital, and the histopathology was reported as Follicular Carcinoma of thyroid with capsular and vascular invasion, but no extrathyroidal extension. Whole body iodine scan done in 2004 showed a good amount of residual thyroid and metastasis to L4 vertebra. She was ablated with I¹³¹ (dose not known) in May 2004 from the same hospital. Whole body iodine scan done several times after that was reported to be negative. A follow-up scan done on December 2008 in our institute showed metastatic focus in L4 vertebra and a high serum Thyroglobulin of 836.5ng/ml (normal range: 3-42 ng/ml). A whole body PET scan showed focal FDG uptake in L4 vertebra and a new focus in left iliac bone.

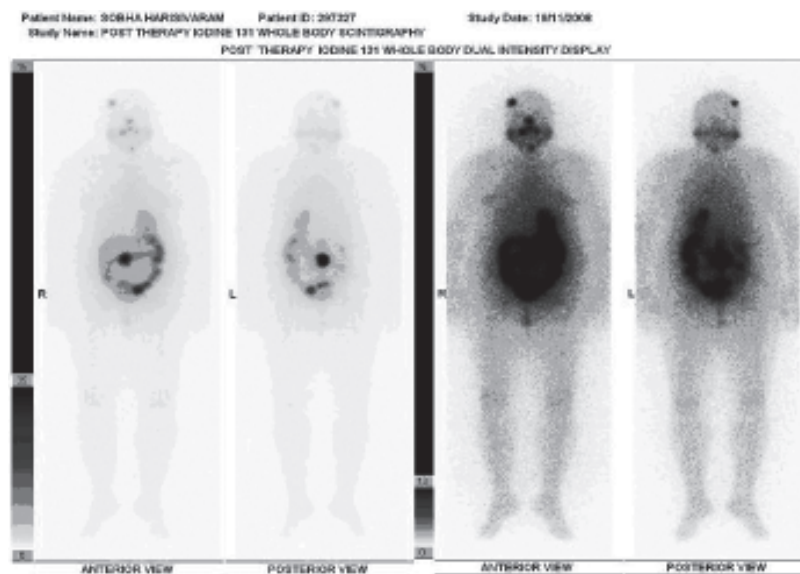
Taking into consideration the L4 vertebra and left iliac bone metastasis with high Thyroglobulin, it was decided to go ahead with the second sitting of high dose I¹³¹ metastasis therapy under steroid cover. Patient was orally ablated with 5624 MBq of I¹³¹ as sodium iodide solution. A post therapy whole body iodine scan showed significant I¹³¹ uptake in L4 vertebral lesion, but no uptake in PET detected left iliac bone lesion. A new focus of significant I¹³¹ was seen in the right parietal bone. There was no any neurological complaints.

Figure 1. Pretherapy iodide scan showing increased uptake in L₄, L₅ vertebrae



The significance of these cases is that, metastasis in some patients behaves differently regarding uptake of I^{131} and FDG-PET. There is a reciprocal or 'flip-flop' relationship between FDG avidity and radio-iodine avidity in metastatic lesions. Well-differentiated thyroid cancers tended to concentrate RAI (but not FDG), while poorly differentiated or anaplastic tumors were highly FDG-avid, but frequently did not concentrate RAI. Some of the FDG-avid lesions also concentrate radioactive iodine (RAI) while others do not. This heterogeneity of tracer avidity could be demonstrated within same patients, suggesting that each metastatic lesion might have its own unique metabolic pattern. Finally, lesions that accumulated FDG are more aggressive in their growth pattern than those that only concentrated RAI.

Figure 2. Post I^{131} therapy whole body scan, showing significant uptake in L_4 , L_5 vertebrae and a new focus of uptake in right parietal skull bone.



Thyroid Watch

Compiled by M G Pillai

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- 1. Risk factors for thyroid cancer in hyperthyroidism:** In a retrospective analysis of 817 thyroidectomies done for hyperthyroidism, thyroid carcinoma was seen in the surgical specimens in 3.8 % patients with Graves' disease, 6.4 % in toxic MNG and 12 % in toxic adenoma. 45 % of these "histological surprises" were in a cold nodule. Age > 50 years and presence of cold nodules were found to be significant risk factors associated with presence of malignancy. *Surgery* 2008 Dec; 144(6):1028-36.
- 2. Metabolic and cardiovascular risk in patients on TSH suppression therapy:** Significantly higher insulin levels and lower HDL cholesterol levels were seen in patients with differentiated thyroid carcinoma and subclinical hyperthyroidism induced by levothyroxine therapy when compared to patients who had undergone thyroid surgery for non-malignant pathology. HDL levels showed negative correlation to LT4 dosage and to BMI. *Thyroid Res* 2008 Sep 29; 1(1):2.
- 3. Bone mineral density and hyperthyroidism:** In hyperthyroid patients, significant increase in BMD (as measured by DEXA) at lumbar spine, femoral neck and total hip was seen after 1 year treatment with antithyroid drugs. Urinary pyridinoline cross-links declined significantly becoming normal with treatment of hyperthyroidism. *Neth J Med* 2008 Nov; 66(10):428-32.
- 4. New ECLIA for TRAb:** A new rapid fully automated electrochemiluminescence immunoassay with a measuring time of 27 minutes was compared with 4 commercially available assays. Intra and inter assay coefficients of variation and sensitivity and specificity showed similar or better results with the new assay. *Thyroid* 2008 Nov; 18(11): 1157-64.
- 5. Methimazole as adjuvant to radio iodine for treatment of MNG:** Methimazole given over a mean period of 2.8 months starting at a dose of 10-20 mg led to significant increases in radio iodine tracer uptake compared to that at baseline. There was significant reduction in thyroid volume 1 year after I 131 administration. Eight of the 9 elderly female patients studied had subclinical hyperthyroidism at baseline. Five were hypothyroid at the end of the study. *Expert Opin Investig Drugs* 2008 Dec; 17(12): 1781-6.
- 6. Thyroid dysfunction after treatment for laryngeal cancer:** In a prospective study of 75 male patients followed for an average of 28.6 months after laryngectomy and radiotherapy for laryngeal cancer, the incidence of hypothyroidism was 49.3 percent, the average time of detection being 6 months after completion of treatment. Radiotherapy dose, type of laryngectomy, extent of neck dissection, implementation of thyroid lobectomy, and presence of thyroiditis in specimens were found to be risk factors for thyroid dysfunction. *Otolaryngol Head Neck Surg* 2008 Dec; 139(6):787-91.
- 7. Increased incidence of thyroid cancer may be because of increased pathologic detection:** In a retrospective study of 2,260 patients who underwent surgery for retrosternal goiter over a period of 40 years, the percentage of patients found to have thyroid cancer increased from 3.6 to 7.5%; but, once papillary microcarcinomas (PMC) were excluded there was no increase in cancer incidence. The increase in

the number of PMCs was associated with the increase in the routine number of blocks sampled over the 40-year time period. *Surgery* 2008 Dec;144(6):1038-43

8. **Additional incisions may be needed with the cervical collar incision for removal of retrosternal goiter:** Among 52 patients who underwent thyroidectomy for retrosternal goiter via a collar incision, additional incisions were necessary in 11 patients: a partial sternotomy in 4, total sternotomy in 5, and right thoracotomy in 2. Recurrent nerve paralysis developed in two patients and one patient had a tracheal laceration. *Surg Today* 2008;38(12):1072-7.
9. **Thyroid function and blood pressure in euthyroid individuals:** In a cross-sectional study, TSH and the “fT4.TSH product” (suggested as a T4 resistance index) were positively associated with diastolic pressure. The “fT4.TSH product” was found to be a significant predictor of diastolic pressure independently of HOMA-IR and BMI. *Thyroid Res* 2008 Sep 29;1(1):3.
10. **Childhood obesity and thyroid structure and function:** Obese children when compared to age and sex matched controls showed alterations in thyroid structure resembling Hashimoto’s thyroiditis (as assessed by ultrasound) and thyroid function even in the absence of antithyroid antibodies. *JCEM* 2008;93 (12), 4749-4754.

Correspondence

Thyrotoxicosis and thrombocytopenia – an uncommon association

TK Sabeer

To the Editor :

This is in reference to the case report by S Kannan et al titled “Thyrotoxicosis and thrombocytopenia – an uncommon association” published in Thyroid research and practice journal in Vol: 5, No: 2, May- August 2008 issue.

This particular case report exemplified the possible non immune mechanisms involved in the causation of thrombocytopenia during thyrotoxicosis and the need for testing thyroid dysfunction in cases of autoimmune diseases like idiopathic thrombocytopenic purpura (ITP), especially when response to conventional treatment is poor. Majority of patients with ITP improve when the thyroid disease is under control by medical, surgical or radio-iodine ablation. Also the conventional treatment for ITP such as steroids or immunoglobulin may be ineffective in the absence of effective treatment for thyrotoxicosis

I would like to report a similar case who had a different mode of presentation than the one described by S Kannan et al. A 55 year old post menopausal woman was diagnosed with Grave’s disease in August 2007 with a TSH of less than 0.005 mIU/mL, free T4 of 3.29 ng/dL and increased iodide uptake on radioisotope scan. She was started on methimazole 20 mg/day and beta blockers. She was doing well for initial two months and in october 2007, she presented with purpuric rashes, thrombocytopenia (Platelet count 53,000/mm³) and other cell lines were normal. She was evaluated by Hematologist and was started on prednisolone. She improved gradually and steroid dose was tapered. She is presently euthyroid and is on 5mg/day of methimazole and 5 mg/day of prednisolone and has a platelet count of 25,000/mm³.

This case is notified to highlight the incidence of thrombocytopenia in patients with Grave’s disease which probably has the same immunological cause and genetic predisposition of underlying autoimmune disease. It is to be noted that in this particular case thrombocytopenia presented after the onset of Grave’s disease and the patient was treated with anti thyroid medications as compared to Radio Iodine ablation in the case described by S Kannan et al.

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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 separate 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.
3. Goldberg RB, Mellies MJ, Sacks FM, et al. Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels: subgroup analyses in the cholesterol and recurrent events (CARE) trial. The Care Investigators. *Circulation* . 1998;98:2513-9.
4. Boyages SC. Primary pediatric hypothyroidism and endemic cretinism. In: Bardin CW, ed. *Current therapy in endocrinology and metabolism*. 5th Ed. S t. Louis: Mosby, 1994:94-8.


Units of Measurement

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

For any further clarifications, the authors may correspond with the editor, or visit the website: www.icmje.org, where the uniform requirements for manuscripts submitted to biomedical journals are described more exhaustively.




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