International Journal of Science and Research (IJSR)
ISSN: 2319-7064
ResearchGate Impact Factor (2018): 0.28 | SJIF (2018): 7.426

Adenomatous Goiter with Hyperthyroidism in 12 Years Old Female

Wega Upendra Sindhughosa[1], I Made Arimbawa[2]

[1-3] Child Health Department, Medical School, Udayana University/Sanglah Hospital Denpasar, Indonesia

Abstract: ***Background: Hyperthyroidism is a condition in which the thyroid overproduces hormones and associated with a complex physiological and biochemical condition. Hyperthyroidism in children is often caused by toxic thyroid nodule and toxic adenoma, and very rarely caused by adenomatous goiter with incidence only 1, 5%. Case Presentation Summary: We report a 12 years old female with adenomatous goiter hyperthyroidism. The patient's complained of feeling exhausted and there were weight loss in last 3 months. From physical examination body weight is 35 kg (percentile 10-25 CDC 2000), body height 144cm (percentile 10-25 CDC 2000), head circumference 52,5cm (Mean 50% nellhaus). There is a solid mass in the neck, fixed, no redness, tenderness nor signs of inflammation. From laboratory examination revealed thyroid hormone increased with FT4 60,3 ng/dl (0.93-1.70 ng/dl) while TSH decreased in 0,05 IU/ml (0.27-4.20IU/ml), TRAb (-). USG examination showed solid mass with cystic degeneration, CT-scan of head and midface showed cystic solid mass with central necrotic calcification. Fine needle aspiration biopsy showed cytomorphology according to follicular neoplasms with cystic degeneration and biopsy of the nodule showed adenomatous goiter. Patient underwent for total thyroidectomy and after one week post operation the thyroid hormone decline and patient planned for lifelong treatment of thyroid hormone replacement. Summary: Hyperthyroid caused by adenomatous goiter is a very rare case. The manifestation including symptoms and sign of hyperthyroid with biopsy showed adenomatous goiter..***

Keywords: Adenomatous goiter, Hyperthyroidism

1. Introduction

Thyroid nodules are rare in children affecting 1% to 2% of the pediatric population.[1],[2] These nodules are less common in children compared to adults, but often related to malignancy; as high as 26% cases in pediatric are related to malignancy while in adults the rate is ranged between 5-10%.[3],[4] Management of these lesions tends to be more aggressive owing to a perceived increasing risk of malignancy in the pediatric population, particularly for younger patients with thyroid nodules.[5]

Hyperthyroidism is a disorder that rarely found in children, but this number increases in adolescence and adulthood. In children, 95% of hyperthyroidism is caused by Graves' disease and very rarely caused by adenomatous goiter. Hyperthyroidism is a different term with thyrotoxicosis.[1] Thyrotoxicosis is a general term referred to a condition of elevated levels of T3 (triiodothyronine) and / or T4 (thyroxin) with any causes, whereas hyperthyroidism referred to the cause of a specific thyrotoxicotic state resulting from an increase in thyroid hormone production that leads to increased metabolism in peripheral tissue.[6]

Low incidence rates and unspecific early symptoms are among the causes of pediatric patients with hyperthyroidism often not an initial priority in determining differential diagnoses by health practitioners.[7],[8] Often pediatric patients with hyperthyroid wait for several months until their diagnosis is established.[6],[7] The exact incidence rate of hyperthyroidism in children in Indonesia cannot be determined. Some studies abroad estimates the overall incidence rate ranging from 1/100,000 children per year.[5] 0.1/100,000 children per year for children 0-4 years, increased up to 3/100,000 children per year by adolescence.[9],[10] The prevalence in women is 6-8 times greater than in adolescent man.[8]

Adenomatous goiter is an enlargement of the encapsulated thyroid gland, either single or multiple. Enlargement of the thyroid gland can lead to eutyroid state and can also cause a state of increased production of thyroid hormone.

2. Case

Female patient, 12-years-old, came with a lump in the neck. The lump appears on the left and right neck. The size of the lump originally about the size of beans starting at 1 year old then gradually enlarged. Patient is a children who is active, complain of frequent sweating, and often feel tired, patients also complain difficult to concentrate. Based on heteroanamnesis to the patient's parents, the patient's development is within normal limits. Patient had previous medical history at RSUD Karangasem and has been given propylthiouracil treatment for 1 month, then on November 17, 2015 the patient was referred to the surgical polyclinics of Sanglah Hospital.

Patients had no history of tumor or cancer in the family. Patient is the third child of 4 siblings, the patient has twin siblings. Patient was born term, spontaneous in midwife, birth weight 1500 gram, no congenital abnormalities. The patient's diet for 24 hours suitable with the total daily caloric requirements.

Physical examination of the patient obtained that patient is fully conscious, blood pressure 110/70 mmHg (P90:116/75), heart rate 80 beat/minutes, respiration rate 23 time/minutes, body temperature 36.8^0C, vital signs within normal limits. The patient body weight 35 kg and 144 cm in height. Based on growth curve of CDC 2000 of BW/A (P_{10-25}), BH/A (P_{10-25}), BW/BH (P_{10-25}), ideal weight 37 kg, upper segment/lower segment ratio 1.02. On neck examination, a lump in the neck area is found with size 4x5x4 cm, solid consistency, flat surface, fixed with surrounding tissue, no

pain when pressed, no signs of inflammation. there is no exophthalmos in the eye, . Ear, nose, and throat within normal limit. Chest form and movement symmetrical, vesicular breath sounds without rhonchi and wheezing, normal heart sound, regular, no murmurs. Abdominal examination of bowel sounds within normal limits, palpation of soufflé, and no abdominal distension. Hepar and lien are not palpable enlarged. Extremities within normal limits. Neurologic examination showed that power, tone, reflexes are within normal limits

Laboratory examination by complete blood count is within normal limits with hemoglobin 13.2 g/dl, hematocrit 39.52%, leukocyte 9.17/mm^3, platelet 373.5/mm^3. The liver function test is within normal limits with serum aspartate transaminase (AST) 27.8 U/L (11-27 U/L), alanine aminotransferase (ALT) 20.0 U/L (11-34 U/L), electrolytes in normal limits with sodium 136 mmol/L, potassium 3.69 mmol/L, chloride 102.9 mmol/L, Calcium 9.68 mg/dl. Renal function results within normal limits with BUN 8.0 mg/dl, creatinine 0.36 mg/dl, from thyroid function showed FT4 60.3 ng/dl (0.93-1.70 ng/dl) while TSH 0.05 IU/ml (0.27-4.20IU/ml). Antithyroid antibodies (TRAb) showed negative result.

From thorax X-ray it can be concluded there is a soft tissue mass on right and left of the neck, the mass cause right deviation of the trachea and upper right widening of mediastinum.

Thyroid ultrasound examination showed solid mass with cystic degeneration in the left right lobe and thyroid isthmus, Fine Needle Aspiration Biopsy (FNAB) obtained cytomorphological results suitable for Follicular Neoplasm with cystic degeneration.

CT scans of the midface and colli performed and obtained solid cystic mass results with calcification and central necrotic in it in the right lobe of the thyroid attached to the trachea and partially into the thoxic inlet (T4aNxMx).

Bone age examination revealed 12 years old (average) Histomorphology in Pathologic anatomy examination showed struma adenomatous.

Based on historical anamnesis, physical examination, and additional investigation patient diagnosed with hyperthyroid adenomatous Struma. In this patient, the management total thyroidectomy was performed and then the patient received eutyrox 100ug per day.

3. Discussion

The normal thyroid gland is a fairly homogenous structure, but nodules often form within its substance. These nodules may be only the growth and fusion of localized colloid-filled follicles, or more or less discrete adenomas, or cysts. Children with thyroid enlargement could present with or without symptoms of thyroid excess or deficiency. Symptoms are generally insidious in onset, which may delay the diagnosis by weeks or months.[3] Nodules larger than 1 cm may be detected clinically by palpation. Careful examination discloses their presence in at least 4% of the general population. Nodules less than 1 cm in diameter not clinically detectable unless located on the surface of the gland, are much more frequent. The terms adenomatous goiter, nontoxic nodular goiter, and colloid nodular goiter are used interchangeably as descriptive terms when a multinodular goiter is found. In this case the patient is 12 years old girl presents with symptoms of a palpable mass in the neck. The mass appears on the left and right neck. The size of the mass originally about the size of beans then enlarged within a month.

Based on physical examination, according to WHO classification, goiter can be classified as follows:

- Grade 0: no goiter presence is found (the thyroid impalpable and invisible);
- Grade 1 (a): neck thickening is present in result of enlarged thyroid, palpable, however, not visible in normal position of the neck; the thickened mass moves upwards during swallowing. Grade 1 includes also nodular goiter if thyroid enlargement remains invisible.
- Grade 1 (b): Noticeable gland on neck hyperextension
- Grade 2: neck swelling, visible when the neck is in normal position, corresponding to enlarged thyroid – found in palpation.
- Grade 3: visible gland at a distance of 10 meters.

In this case patient was classified into goiter grade 3 according to WHO classification.

Many of the symptoms of multinodular goiter have already been described. They are chiefly due to the presence of an enlarging mass in the neck and its impingement upon the adjacent structures. There may be dysphagia, cough, and hoarseness. Paralysis of recurrent laryngeal nerve may occur when the nerve is stretched out across the surface of an expanding goiter, but this event is very unusual. When unilateral vocal cord paralysis is demonstrated, the presumptive diagnosis is cancer. Pressure on the superior sympathetic ganglions and nerves may produce a Horner´s syndrome.

As the gland grows it characteristically enlarges the neck, but frequently the growth occurs in a downward direction, producing a substernal goiter. A history sometimes given by an older patient that a goiter once present in the neck has disappeared may mean that it has fallen down into the upper mediastinum, where its upper limits can be felt by careful deep palpation. Hemorrhage into this goiter can produce acute tracheal obstruction. Sometime substernal goiters are attached only by a fibrous band to the goiter in the neck and extend downward to the arch of the aorta. They have even been observed as deep in the mediastinum as the diaphragm. Occasionally the skilled physician can detect a substernal goiter by percussion, particularly if there is a hint from tracheal deviation, or the presence of a nodular mass in the neck above the manubrial notch. In this case the symptoms were previously unspecific, such as sweating, appeared to be more active, difficulty in concentrating. There was no growth

impairment, a palpable mass in the neck. The mass appears on the left and right neck.

Clinical symptoms and investigations in the diagnosis of single nodular goiter
Symptoms and signs
Often family history of benign thyroid disease
Slowly growing anterior neck mass
Uni- or multinodularity on examination
Enlargement during pregnancy
Cosmetic complaints
Asymmetry, tracheal deviation, and/or compression
Rarely upper airway obstruction, dyspnea, cough, and dysphagia
Sudden transient pain or enlargement secondary to hemorrhage
Gradually developing hyperthyroidism
Superior vena cava obstruction syndrome (rare)
Recurrent nerve palsy (rare)
Horner´s syndrome (rare)
Investigations
TSH normal or decreased, normal free T4, and free T3,
Serum Tg usually elevated
Thyroid autoantibodies (TPO and Tg) usually negative
Scintigraphy with solitary or multiple hot and/or cold areas
Ultrasound finding of solitary or multiple nodules with varying echogenicity (nonhomogeneity)
Computed tomography and MR imaging demonstrating solitary or
multiple nodules with varying echogenicity
Lung function testing may demonstrate impaired inspiratory capacity
Fine-needle aspiration of solitary or dominant nodules – benign cytology

Pathophysiology

Genetic heterogeneity of normal follicular cells and acquisition of new inheritable qualities by replicating epithelial cells. It has been shown cells of many organs, including, the thyroid gland, are often polyclonal, rather than monoclonal of origin. Also from a functional aspect it appears that through developmental processes the thyroid epithelial cells forming a follicle are functionally polyclonal and possess widely differing qualities regarding the different biochemical steps leading to growth and to thyroid hormone synthesis like e.g. iodine uptake (and transport), thyroglobulin production and iodination, iodotyrosine coupling, endocytosis and dehalogenation. As a consequence there is some heterogeneity of growth and function within a thyroid and even within a follicle Studer et al demonstrated the existence of monoclonal and polyclonal nodules in the same multinodular gland.[11],[12],[13] They analyzed 25 nodules from 9 multinodular goiters and found 9 to be polyclonal and 16 monoclonal. Three goiters contained only polyclonal nodules and 3 contained only monoclonal nodules. In 3 goiters poly- and monoclonal nodules coexisted in the same gland.[14]

Heterogeneity of morphology and function in a human multinodular goiter. Autoradiographs of two different areas of typical multinodular euthyroid human goiter excised after administration of radioiodine tracer to the patient. There are enormous differences of size, shape and function among the individual follicles of the same goiter. Note also that there is no correlation between the size or any other morphological hallmark of a single follicle and its iodine uptake.

Newly generated cells may acquire qualities not previously present in mother cells. These qualities could subsequently be passed on to further generations of cells. A possible example of this process is the acquired abnormal growth pattern that is reproduced when a tissue sample is transplanted into a nude mouse.[13] Other examples are acquired variable responsiveness to TSH.[15] These changes may be related to mutations in oncogenes which do not produce malignancy per se, but that can alter growth and function. An example of acquisition of genetic qualities is the identification in the last few years of constitutively activating somatic mutations not only in solitary toxic adenoma, but also in hyper functioning nodules of toxic multinodular goiters.[16] So far these mutations in MNG have only been found in the TSH-receptor (TSHR) gene, and not in the Gs-alpha gene. Different somatic mutations are found in exon 9 and 10 of the TSHR gene and the majority of mutations that are present in toxic adenomas are also found in toxic nodules in multinodular goiter.[17],[19]

In contrast to sporadic goiters, caused by spontaneous recessive genomic variation, most cases of familial goiter present an autosomal dominant pattern of inheritance, indicating predominant genetic defects. Gene-gene interactions or various polygenic mechanisms (i.e. synergistic effects of several variants or polymorphisms) could increase the complexity of the pathogenesis of nontoxic goiter and offer an explanation for its genetic heterogeneity.[20],[24] A strong genetic predisposition is indicated by family and twin studies.[25],[27] Thus, children of parents with goiter have a significantly higher risk of developing goiter compared with children of nongoitrous parents.[24] The high incidence in females and the higher concordance in monozygotic than in dizygotic twins also suggested a genetic predisposition.[22] Moreover, there is preliminary evidence of a positive family history for thyroid diseases in those who have postoperative relapse of goiter, which can occur from months to years after surgery.

Defects in genes that play an important role in thyroid physiology and thyroid hormone synthesis could predispose to the development of goiter, especially in case of borderline or overt iodine deficiency. Such defects could lead to dyshormonogenesis as an immediate response, thereby indirectly explaining the nodular transformation of the thyroid as late consequences of dyshormonogenesis, as a form of maladaptation.[28] The genes that encode the proteins involved in thyroid hormone synthesis, such as the thyroglobulin-gene (TG-gene), the thyroid peroxidase-gene (TPO-gene), the sodium – iodide – symporter-gene (SLC5A5), the Pendred syndrome-gene (SLC26A4), the TSH receptor-gene (TSH-R-gene), the iodotyrosine deiodinase (DEHAL 1) and the thyroid oxidase 2 gene3 (DUOX2) are convincing candidate genes in familial euthyroid goiter.[29] Originally, several mutations in these genes were identified in patients with congenital hypothyroidism.[30] However, in cases of less severe functional impairment, with can still be compensated, a contribution of variants of these genes in the etiology of nontoxic goiter is possible. In this case the patient has not done chromosome examination and there's no history the same disease in family.

The secondary factors discussed below stimulate thyroid cell growth and / or function and, because of differences in cellular responsiveness that are presumed to exist, aggravate the expression of heterogeneity which leads to further growth and focal autonomic function of the thyroid gland. Local necrosis, cyst formation sometimes with bleeding and fibrosis may be the anatomical end stage of such processes.

Pathogenesis of thyromegaly
Stimulation
Thyrotropin (TSH)
Inhibition of hormonogenesis
Excessive pituitary secretion
Thyroid-stimulating antibodies (TSAb)
Infiltration
Neoplastic
Adenoma
Carcinoma
Lymphoma
Histiocytosis
Nonneoplastic
Cysts
Inflamation
Infectious
Bacterial
Viral
Other pathogens
Noninfectious
Lymphocytic (autoimmune) thyroiditis

Pathology

Many studies have found that FNAB is highly sensitive and accurate test in differentiating benign nodule from malignant nodule. Though some consider this procedure of limited usefullnes in children because of its discomfort and rate of side effect, if the procedure is performed properly moreover with ultrasonography guidance, it should have low positive and negative result. The accuracy rate of FNAB has been reported in between 77,2% and 98,6%. The sensitivity of this exam in different studies has ranged from 60% to 100%, specificity has ranged from 63% to 100%. [1],[2]

There is several categorizing systems for FNAB outcomes. The first typically categorizes outcomes into four categories (a) malignant (carcinoma identified); (b) suspicious for malignancy including follicular neoplasm (hyperplastic nodules, follicular adenoma, follicular carcinoma, and follicular variant of papillary carcinoma) and Hurthle cell neoplasm; (c) benign (adenomatous/colloid nodule, macrophages, and aggregates of normal-appearing uniform thyroid cell, and Hashimoto's thyroiditis); and (d) unsatisfactory (cyst fluid or few cells identified). A second outcomes scale that is used is the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC). This scale was developed for the adult population but recently Smith et al. classified cytological findings in children. This classification includes six categories: (a) nondiagnostic/unsatisfactory, (b) benign, (c) atypia of undetermined significance/follicular lesion of undetermined significance, (d) suspicious for follicular neoplasm, (e) suspicious for malignancy, and (f) malignant.[2] In this case, pathology result revealed follicular neoplasm with cystic degeneration.

The graphic term "Puddingstone goiter" has been applied. Frequently the nodules have degenerated and a cyst has formed, with evidence of old or recent hemorrhage and the cyst wall may have become calcified. Often there is extensive fibrosis, and calcium may also be deposited in these septae. Scattered between the nodules are areas of normal thyroid tissue, and often-focal areas of lymphocytic infiltration. Radio autography shows a variegated appearance, with RAI localized sometimes in the adenomas and sometimes in the paranodular tissue. Occasionally, most of the radioactivity is confined to a few nodules that seem to dominate the metabolic activity of the gland.

Differential Diagnosis of Thyromegaly
Etiology of diffuse thyromegaly
Hashimoto thyroiditis
Thyrotoxicosis
Graves disease
Toxic thyroiditis
TSH secreting pituitary adenoma
Pituitary resistance to thyroid hormone
Goitrogen ingestion
Antithyroid drugs
Other antithyroid agents and foods
Iodine deficiency
Dyshormonogenesis
Acute and subacute thyroiditis (bacterial or viral)
Idiopathic (simple) goiter
Etiology of nodular thyromegaly
Hashimoto thyroiditis
Thyroid cyst
Thyroid adenoma
Hyperfunctioning (hot): thyrotoxicosis or euthyroidism
Nonfunctioning (cold)
Thyroid carcinoma
Other thyroid tumors
Nonthyroidal masses
Lymphadenopathy
Branchial cleft cyst
Thyroglossal duct cyst

Laboratory investigation

The choice of tests to investigate the functional status of a patient with a simple diffuse goiter or multinodular goiter may differ depending on the geographic areas of the world. Recent surveys conducted in the American, European and Latin American Thyroid Associations have indicated that the North American thyroidologists are quite restrictive in the choice of laboratory tests. Most of the experts, however, would perform a serum TSH and serum Free T4 test. In other settings Total T4 and Total T3 are also included because of the preferential secretion of T3 over T4 in mild iodine deficiency.[36]

Antibodies against thyro-peroxidase (anti-TPO) and thyroglobulin (anti-TG) are measured, routinely, by most Europeans and Latin Americans thyroidologists. This seems to be relevant because thyroid auto antibodies are found approximately in 10% of the population and, consequently, autoimmunity may coexist with a goiter. Also diffuse or focal lymphocytic infiltration in an enlarged gland may represent chronic autoimmune thyroiditis. Although serum TG correlates with the iodine status and the size of the

enlarged thyroid gland it has little or no value in the diagnosis of goiter.

Hyperthyroidism results from excessive secretion of thyroid hormone and during childhood is mainly due to Graves' disease. Other causes are rare and should be suspected only when there is an atypical presentation, such as negative in Thyroid Stimulating Immunoglobulin examination. Other rare causes of hyperthyroidism that have been observed in children include toxic uninodular goiter (Plummer disease), hyperfunctioning thyroid carcinoma, thyrotoxicosis factitia, subacute thyroiditis, and acute suppurative thyroiditis. Autonomously hyperfunctioning adenomas secrete T3 and cause varying degree of hyperthyroidism. The thyroid is usually of small or normal size with a palpable nodule. Symptoms of hyperthyroidism generally occur when the nodule is greater than 2.5 cm in diameter.[5] In this case, the laboratory investigation revealed increasing of free thyroxin (FT4), and decreasing of thyrotropin (TSH), while examination of TSH receptor antibodies (TRAb) revealed to be negative.

Goiter is frequently the first indicator of thyroid disease in children with or without symptoms of thyroid hormone deficiency or excess. Thyroid nodules in children are unusual but are more often malignant than those in adults. Thyroid palpation has a low accuracy for the detection of thyroid nodules and a high false-negative rate for the small non-palpable nodules.[37] By contrast, false-positive results occur frequently in the presence of autoimmune thyroid disease, in which lobular asymmetry or an uneven glandular surface may be interpreted as a nodule on palpation. Ultrasonography is a useful tool for the evaluation and characterization of nodular thyroid disease.

Ultrasonography may detect non palpable nodules cysts, will estimate nodule and goiter size (volume), will monitor the changes following therapy and will guide the Fine Needle Aspiration Biopsy (FNAB). After the introduction of ultrasonography it has become clear that nodules in the thyroid gland are very prevalent, ranging from 17% to 60% if older people are included in the study (85-95). Hypo echogenicity, micro-calcifications, indistinct borders, increased nodular flow (visualized by DOPPLER) may have predictive value in distinguishing malignant from benign nodules (even in Multinodular Goiters). In this case**,** Ultrasonography examination revealed solid mass with cystic degeneration in right, left lobe and isthmus.

The surgical procedure for bilateral multinodular nontoxic goiter (BMNG) remains controversial. Delbridge reported that subtotal thyroidectomy for benign thyroid disease has been performed for more than a century and that it may reduce the associated risk of postoperative hypocalcemia and recurrent laryngeal nerve (RLN) palsy.[38] However, it usually leads to high recurrence for BMNG patients in the long-term follow-up. TT has become a preferred surgical procedure for BMNG for the majority of surgeons because it eliminates the risk of recurrence and there is no need reoperation for incidental differentiated thyroid cancer.[39] However, this radical procedure may increase the risk of iatrogenic injury.[40] TT is a feasible and safe procedure for patients with BMNG. Although TT involves a significantly higher risk of postoperative transient hypoparathyroidism, it has a lower recurrence rate than BST.

4. Summary

Female patient, 12-years-old, came with a lump in the neck. The lump appears on the left and right neck. The size of the lump originally about the size of beans then enlarged. Currently the lump is 5 cm in diameter, symmetrical, solid consistency, flat surface, fixed to surrounding tissue, painless when pressed, felt warm. Patient is a children who is active, complain of frequent sweating, and often feel tired, patients also complain difficult to concentrate. FT4 thyroid function test 60.3 ng/dl whereas TSH 0.05 IU/ml, TRAb (-) examination of thorax X-ray showing there is a soft tissue mass on right and left colli causing right deviation of the trachea and upper right widening of mediastinum. Thyroid ultrasound obtained solid mass with cystic degeneration in the left right lobe and thyroid isthmus. CT Scans of Midface and colli obtained solid cystic mass results with calcification and central necrotic in it in the right lobe of the thyroid attached to the trachea and partially into the thoxic inlet (T4aNxMx). Patients with diagnosis of adenomatous goiter hyperthyroidism, then performed total thyroidectomy in the patient, and receives thyroid hormone (eutyrox) 100 ug per day.

References

[1] Tunbridge WGM, Evered DC, Hall R, Appleton D, Brewis M, Clark F et al: The spectrum of thyroid disease in a community: The Whickham survey. Clin Endocrinol; 1977.7:481,
[2] Charib TGH, Thyroid incidentalomas: management approaches to non palpable nodules discovered incidentally on thyroid imaging. Ann Int Med; 1997.126:226-231.
[3] Sawin CT, Bigos ST, Land S, Bacharach P. The aging thyroid. Relationship between elevated thyrotropin levels and thyroid antibodies in elderly patients. Am J Med. 1985;79:591.
[4] Wang KW, Sum CF, Tan KT, Ng WY, Cheah JS, A study of non-toxic goiter. Ann Acad Med Singapore; 1990.19:439-442,
[5] Rallison ML, Dobyns BM, Meikle AW. Natural history of thyroid abnormalities: prevalence, incidence, and regression of thyroid diseases in adolescents and young adults. Am J Med. 1991;91:363-370.
[6] Pinchera A, Aghini-Lombardi F, Antonangeli L, Vitti P. Multinodular goiter. Epidemiology and prevention. Ann Ital Chir; 1996.67:317-325.
[7] Jarlob AE, Nygaard B, Hegedus L, Hartling SC, Hansen JM: Oberver variation in the clinical and laboratory evaluation of patients with thyroid dysfunction and goiter. Thyroid; 1998.8:393-398.
[8] Marine D: Etiology and prevention of simple goiter. Medicine; 1924.3:453.
[9] Taylor S: The evolution of nodular goiter. J Clin Endocrinol Metab. 1953;13:1232.

[10] Beckers C, Cornette C: TSH production rate in nontoxic goiter. J Clin Endocrinol Metab. 1971;32:852.
[11] Derwahl M, Studer H. Nodular goiter and goiter nodules: Where iodine deficiency falls short of explaining the facts. Exp Clin Endocrinol Diabetes; 2001.109:250-60.
[12] Studer H, Peter HJ, Gerber H: Natural heterogeneity of thyroid cells: The basis for understanding thyroid function and nodular growth. Endocr Rev; 1989.10:125.
[13] Peter JH, Gerber, Studer H, Smeds S: Pathogenesis of heterogeneity in human multinodular goiter. J Clin Invest. 1992; 1985;76.
[14] Kopp P, Kimura ET, Aeschimann S, et al. Polyclonal and monoclonal nodules coexist with human multinodular goiters. J Clin Endocrinol Metab. 1994;79:134-139.
[15] Berghout A, Wiersing WM, Smits NJ, Touber JL. Interrelationships between age, thyroid volume, thyroid nodularity, and thyroid function in patients with sporadic non-toxic goiter. Am J Med. 1995;89:602-608.
[16] Krohn K, Wohlgemuth S, Gerber H, Paschke R. Hot microscopic areas of iodinedeficient euthyroid goiters contain constitutively activating TSH receptor mutations. J Pathol. 2000;192:37-42.
[17] Holzapfel AP, Fuhrer D, Wonerow P, et al. Identification of constitutively activating somatic thyrotropin receptor mutations in a subset of toxic multinodular goiters. J Clin Endocrinol Metab. 1997;82:4292-4233.
[18] Tassi V, Di Cerbo A, Porcellini A, Papini E, Cisternino C, et al. Screening of thyrotropin receptor mutations by fine-needle aspiration biopsy in autonomous functioning thyroid nodules in multinodular goiters. Thyroid; 1999.9:353-357.
[19] Gabriel EM, Bergert ER, Grant CS, van Heerden JA, Thompson GB, et al. Germline polymorphism of codon 727 of human thyroid-stimulating receptor is associated with toxic multinodular goiter. J Clin Endocrinol Metab84. 1999;3328-3335.
[20] Krohn K, Führer D, Bayer Y, Eszlinger M, Brauer V et al. Molecular Pathogenesis of Euthyroid and Toxic Multinodular Goiter. Endocr Rev. 2005; 26(4):504-24.
[21] Masini-Repiso AM, Cobanillas AM, Bonaventura M, Coleoni AH. Dissociation of thyrotropin-dependent enzyme activities, reduced iodide transport, and preserved iodide organification in nonfunctioning adenoma and multinodular goiter. J Clin Endocrinol Metab. 1994;79:39.
[22] Hegedus L, Bonnema SJ, Bennedbek FN. Management of simple nodular goiter: current status and fature perspectives. Endocr Reviews; 2003.24:102-132.
[23] Krohn K, Paschke R. Progress in understanding the etiology of thyroid autonomy. J Clin Endocrinol Metab. 2001;86:3336-3345.
[24] Brix TH, Hededus L. Genetic and environmental factors in the aetiology of simple goiter. Ann Med 32:153-156.
[25] Brix TH, Kyvik KO, Hedegu¨s L. Major role of genes in the etiology of simple goiter in females: a population-based twin study. J Clin Endocrinol Metab. 1999;84:3071-3075.
[26] Brix TH, Kyvik KO, Hegedüs L. A population-based study of chronic autoimmune hypothyroidism in Danish twins. J Clin Endocrinol Metab. 2000;85:536-539.
[27] Medeiros-Neto G, Camargo RYC, Tomimori EK. Approach to and treatment of goiters. Med Clin N Am; 2012.92(2):351-358.
[28] Smeulers J, Docter R, Visser TJ, Hennemann G: Response to thyrotrophinreleasing hormone and triiodothyronine suppressibility in euthyroid multinodular goiter. Clin Endocrinology; 1977.7:389.
[29] Knobel M & Medeiros-Neto G: An outline of inherited disorders of the thyroid hormone generating system. THYROID; 2003.13:771-801.
[30] Bignel GR, Canzian F, Shayeghi M, Stark M, Shugart YY, Biggs P, et al. Familial nontoxic multinodular thyroid goiter locus maps to chromosome 14q but does not account for familial nonmedullary thyroid cancer. Am J Hum Genet. 1997;61:1123-1130.
[31] Neumann S, Willgerodt H, Ackermann F, Reske A, Jung M, Reis A, et al. Linkaged of familial euthyroid goiter to the multinodular goiter-1 locus and exclusion of the candidate genes thyroglobulin, thyroperoxidase and NA+/Isymporter. J Clin Endocrinol Metab. 1999;84:3750-3756.
[32] Mckay JD, Williamson J, Lesueur F, Stark M, Duffield A, Canzian F, et al. At least three genes account for familial papillary thyroid carcinoma: TCO and MNG1 excluded as susceptibility loci form a large Tasmanian family. Eur J Endocrinol. 1999;141:122-125.
[33] Capon F, Tacconelli A, Giardina E, Sciacchitano S, Bruno R, Tassi V, et al. Mapping a dominant form of multinodular goiter to chromosome Xp22. Am J Hum Genet. 2000;67:1004-1007.
[34] Bayer Y, Neumann S, Meyer B. Genome-wide Linkage Analysis reveals evidence for four new susceptibility foci for familial euthyroid goiter. J Clin Endocr Metab. 2004;89:4044-53.
[35] Corval M, Perez R, Sanchez I, Mories MT, San Millan JL, Miralles JM, et al. Thyroglobulin gene point mutation associated with non-endemic simple goiter. Lancet; 1993.341:462-464.
[36] Medeiros-Neto G and Knobel M. iodine deficiency disorders. In: deGroot LJ, Jameson JL, eds. Endocrinology 6th Ed. Chapter 88. New York, Elsevier; 2010.
[37] Muirhead S. Diagnostic approach to goitre in children. Paediatr Child Health; 2010.6:195–199
[38] Delbridge L: Total thyroidectomy: the evolution of surgical technique. ANZ J Surg. 2003; 73: 761–768.
[39] Agarwal G, Aggarwal V: Is total thyroidectomy the surgical procedure of choice for benign multinodular goiter? An evidence-based review. World J Surg. 2008; 32: 1313–1324.
[40] Thomusch O, Machens A, Sekulla C, et al: Multivariate analysis of risk factors for postoperative complications in benign goiter surgery: prospective multicenter study in Germany. World J Surg. 2000; 24: 1335–1341.
[41] Hung W, August GP, Randolph JG, et al. Solitary thyroid nodules in children and adolescents. J Pediat Surg. 1982; 17(3):225-9.
[42] Hung W. Nodular thyroid disease and thyroid carcinoma. Pediatr Ann. 1992; 21(1):50-7.

[43] Stevens C, Almahmeed H, Blair G, et al. The Canadian pediatric thyroid nodule study: an evaluation of current management practices. J Pediatr Surg. 2008; 43(5):826-30.
[44] Hegedus L. The thyroid nodule. N Engl J Med. 2004;351(17):1764-71.
[45] Niedziela M. Pathgenesis, diagnosis and management of thyroid nodules in children. Endocr Relat Cancer. 2006; 13(2):427-53.