

Original Article

Multi-nodular goiter: Epidemiology, Etiology, Pathogenesis and Pathology

Ameet V Khatawkar¹, Shreeharsha Mallappa Awati^{2*}

¹Assistant Professor, Department of General Medicine, Karnataka Institute of Medical Sciences, Hubballi, Karnataka, India

²Department of Urology, Sanjay Gandhi Institute of Trauma and Orthopedics, Bangalore, India

*Corresponding author email: awatism@gmail.com

	International Archives of Integrated Medicine, Vol. 2, Issue 9, September, 2015. Copy right © 2015, IAIM, All Rights Reserved. Available online at http://iaimjournal.com/	
	ISSN: 2394-0026 (P)	ISSN: 2394-0034 (O)
	Received on: 10-08-2015	Accepted on: 18-08-2015
	Source of support: Nil	Conflict of interest: None declared.

Abstract

Multi-nodular goiter is a common endocrine disorder worldwide. It is endemic in certain populations. It is more common in women and presents mainly in 4th and 5th decades of life. Various factors have been implicated for the development of multi-nodular goiter, most common being Iodine deficiency. Nodular goiter results from uni or multifocal hyperplasia of follicular cells which may have autonomy of growth and autonomy of function. The process can be divided into five stages which result in the classic appearance and histology of multi-nodular goiter. Present article deals with epidemiology, etiology, pathogenesis and pathology of multi-nodular goiter based on relevant articles searched on pubmed.

Key words

Endemic goiter, Goitrogen, Iodine, Multi-nodular goiter, Radiation, Thyroid, Thyroid follicle.

Introduction

Goiter, or the enlargement of the thyroid gland, comprises a variety of conditions. Goiters can be classified as toxic or non toxic, diffuse or nodular and solitary or multiple [1]. Multi-nodular goiter is a commonly used term describing an enlarged thyroid gland with multiple areas of nodularity [1]. Histologically, MNG is defined as a thyroid enlargement with follicles that are morphologically and functionally grossly altered: it usually develops over years [2]. MNG is

endemic in certain regions of world, mostly in regions of Iodine deficient diet [3]. Various factors are implicated in the development of MNG [4, 5]. Since MNG develops over several years, it is essential to know the etiology and pathogenesis so that preventive measures may be employed to halt its development. In the present article epidemiology, etiology and pathology of MNG are reviewed to help clinicians to implement preventive measures.

Epidemiology

MNG is the most common endocrine disorder affecting 500 to 600 million people worldwide [1]. In India about 54 million people have goiter and the number at risk is estimated to be about 167 million [4]. MNG is said to be endemic when it affects more than 10% of a given population [3]. Annual incidence in non endemic regions is 0.1% to 1.5% and prevalence remains between 4 - 6%. Non endemic goiter is more common in women and elderly [6]. An average figure for sex distribution in both endemic and non endemic regions is 3:1 (Female: Male) [3]. Nodules appear early in endemic goiter and later in sporadic goiters although patient may be unaware of the goiter until his or her late 40s and 50s [7]. In India, main endemic goiter belt is sub Himalayan region and pockets of endemic goiter are present in many states [4].

Etiology

A). **Iodine deficiency:** It is the most common cause of goiter. This may be due to low iodine content in water and food or due to failure of intestinal absorption [7]. Goiter occurs if Iodine intake is <50 µg/day [4].

B). **Dyshormonogenesis:** Uncommon cause of non toxic goiter and six separate intrathyroidal disturbances have been incriminated in dyshormonogenesis [5].

- Defects of iodine trap.
- Defects of organification - most common defect.
- Defect of coupling.
- Protease enzyme deficiency.
- Synthesis of abnormal iodoproteins.

The development of goiter in these patients depends on severity of defect and environmental factors. Environmental factors may compensate in areas of high iodine intake and may precipitate in areas of iodine deficiency.

C). **Goitrogens:** By blocking steps in thyroid hormone synthesis or inhibiting iodine uptake cause a hyperplastic gland with compensated thyroid function [5].

- **Drugs:** Thiocarbamides (Antithyroid drugs), Chlorpropamide, PAS,

Amiodarone, Glutathiamide, Reserpine, Phenylbutazone, Lithium, Large doses of Iodine, Sulfonylureas, Calcium [4].

- **Food:** Vegetables of brassica family [cabbage, kale, Rape] Turnips, Soyabean flour, Cassava [4]. Cabbage contains thiocyanates which inhibit iodine uptake.
- **Radiation:** Previous thyroid irradiation increases the incidence of both benign and malignant nodules in the gland [1]. The malignancy risk in a palpable nodule in these circumstances ranges from 20% to 50%. The dose range is 400-1500 rads and time taken for development of nodular thyroid disease after exposure to radiation ranges from 6 to 35 years mainly at 30 years. Radiation causes increased stimulation of thyroid epithelium by TSH especially in presence of goitrogens and effect is much more in children, who have active proliferation of the gland. Higher radiation dose destroys thyroid gland and causes hypothyroidism rather than nodular disease or malignancy. External radiation is the most important environmental risk factor for thyroid malignancy. Among survivors of Hiroshima and Nagasaki radiation exposure, the incidence of thyroid cancer is higher and the relative risk is higher for patients who were younger and who had acute radiation exposure. Chronic, low dose exposure doesnot has the same risk [2].

D). **Genetic influences:**

- A gene located on chromosome 14q dubbed MNG-1 has been associated with familial non toxic MNG.
- Polymorphism of codon 727 has been associated with toxic MNG [1].

Pathogenesis

Nodular goiters result from focal hyperplasia of follicular cells at one site or, most often at multiple sites within the thyroid gland. The basic process in goitrogenesis is the generation of new

follicular cells, which are used either to form new follicles or to enlarge the size of newly formed follicles. The sprouting of a capillary network embedded in stromal cells is a necessary secondary event [8].

The driving force behind multi-nodular goiter growth is an intrinsically abnormal growth potential of a small fraction of all thyroid cells. Extra thyroidal factors such as TSH, may act upon this basic process and thereby accelerate goiter growth [8].

Generation of heterogeneity:

In addition to somatic mutations leading to clonal tumor growth, three basically different phenomenon are involved in the generation of the tremendous regional heterogeneity of growth, structure and function of multinodular goiters [8].

First is the preexisting constitutive heterogeneity of normal follicular epithelial cells which accounts for the highly variable traits of their progeny cells. Normal follicular cells exhibit significant differences in growth potential, peroxidase content and capacity to iodinate thyroglobulin [6].

Second process is the acquisition by replicating follicular cells of new inheritable qualities like abnormal growth pattern and variable responsiveness to TSH.

The third process is the appearance of secondary structural abnormalities such as generation of macrofollicles and microfollicles and altered functions like distorted responses of follicles to TSH.

Growth of the normal thyroid and its transformation into a goiter: TSH is the most important stimulator of thyroid growth and function. Other growth promoting cytokines are insulin like growth factors I and II (IGF) EGF, FGF and growth inhibiting cytokine, transforming growth factor (TGF). Local production of these factors is altered in nodular

goiters; e.g. IGF is produced by autonomously growing thyroid nodules. Multi-nodular goiter is a multifocally growing benign tumor of the thyroid gland. Growth of nodular goiter proceeds by episodic, autonomous replication of a multitude of cell cohorts scattered all over the single nodules and even over extra-nodular tissue. It is on this substrate that extra-thyroidal growth stimulating agents such as TSH (in Iodine deficiency) or growth promoting immunoglobulins may come to act. Any goitrogen (TSH or other factor) involved in the pathogenesis of simple goiter must have two characteristics.

- Its biologic potency or its blood concentration must be well below that of immunoglobulins producing Grave's disease.
- The goitrogen must act over a long period.

Autonomy of growth:

Normal thyroid glands contain subpopulation of follicular cells with a constitutively high growth potential. Such cells divide even in absence of TSH and in presence of TSH or goitrogen may divide at faster rate and take a larger share of follicular cell population and once present in large enough numbers, whole thyroid or parts thereof may grow autonomously even in the absence of extra-thyroidal stimulation.

Autonomy of function:

Normal thyroid contains subpopulation of cells with higher iodinating capacity. If new follicles develop from such cells, they have a higher level of function which is less suppressible by abolition of TSH secretion.

Autonomous function and autonomous growth are separate features of individual follicular cells and hence there is no correlation between nodule size and toxicity. Cold areas of a nodular goiter have same growth potential as hot ones. The pathogenesis of nodule formation in multi-nodular goiters may be caused by three basically different processes [6].

The first one is the presence of cell subsets with higher autonomous growth rate. These cells with rapid replication eventually account for a large percentage of entire follicular cells population, resulting in apparent nodules.

A second mechanism is the formation of fibrous tissue within the thyroid as a result of follicular necrosis and hemorrhage that occurs when vascular supply cannot keep pace with the expanding parenchyma.

The third mechanism is due to somatic mutations resulting in a single progeny cell line with a preferential growth advantage and subsequent well encapsulated nodules that are often single or few in numbers.

Somatic mutations known to occur in thyroid follicular cells include ras oncogenes, G proteins, and mutations in the TSH receptor gene resulting in hyper functioning adenomas.

The evolution of Nodular Goiter (The Natural history of simple goiter) [7]: There are five stages in goiter formation as proposed by Selwyn Taylor [9].

Stage 1: Simple diffuse enlargement of the thyroid-Persistent growth stimulation causes diffuse hyperplasia; all lobules are composed of active follicles and iodine uptake is uniform. This stage may persist for a longtime but is reversible if stimulation ceases.

Stage 2: Areas of local hyper function - As a result of fluctuating stimulator, a mixed pattern develops with areas of active lobules and areas of inactive lobules.

Stage 3: Hyper active nodules showing hemorrhage and necrosis-Active lobules become more vascular and hyper plastic until hemorrhage occurs causing central necrosis and leaving only a surrounding rim of active follicles.

Stage 4: Inactive nodules - Necrotic lobules coalesce to form nodules filled either with iodine, free colloid or a mass of new but inactive follicles.

Stage 5: Multi-nodular Goiter - Continual repetition of this process results in a nodular

goiter. Most nodules are inactive, and active follicles are present only in inter nodular tissue.

Pathology of multi-nodular goiter [10]

Grossly, the thyroid is enlarged and distorted. The size of the lobes differs considerably. The surface of the gland shows a knobby configuration confined by a stretched but intact capsule. The cut surfaces disclose multiple various sized nodules, some of which may be partially or completely encapsulated, others being devoid of capsules and more or less well demarcated from the surrounding parenchyma. Whitish fibrous bands, sometimes calcified separate the nodules or traverse them. Colloid rich nodules are gelatinous with a yellowish, tanred-brown, translucent appearance. More cellular nodules appear fleshy or rubbery. Degenerative changes like signs of fresh or old hemorrhage, necrosis with fibrosis, cholesterol deposition, calcifications and cyst formation are common.

Histology [1]

The initial histologic pattern is diffuse hyperplasia that is later followed by colloid storage in a nodular pattern. The chronic multi-nodular goiter is described as heterogeneous nodularity within the thyroid gland that is commonly incompletely encapsulated, whereas the follicles of various sizes are morphologically and functionally identical to the normal thyroid tissue. These nodules may have colloid or clusters of smaller follicles surrounded by a fibrous stroma, possibly with lymphoid infiltration. Larger nodules develop pseudo-capsules that usually incompletely encapsulate and merge into surrounding stroma. Overgrowth of nodules and expansion with resultant scarring from multiple episodes of hemorrhagic necrosis within areas of non-elastic connective tissue are also present.

Toxic multi-nodular goiter: The thyroid tissue between nodules may show hyper plastic changes, frequently lymphoid infiltration is present in the stroma. Nodules may show oxyphil

or even clear cell changes. In some cases both nodules and inter nodular parenchyma show intense epithelial hyperplasia [10].

Conclusion

MNG is a common thyroid disorder. It is endemic in iodine deficient regions. It develops slowly over decades. Radiation, genetics, enzyme deficiencies, certain drugs and other diet factors have also been implicated in the causation of MNG. The pathogenesis has been divided into five stages. Autonomy of growth and function are responsible for clinical picture of MNG. Knowledge about these factors has led to preventive interventions such as iodination of salt and has led to decreasing incidence of nodular goiter.

References

1. Day TA, Chu A, Hoang K. Multinodular goiter. *Otolaryngol Clin N Am.*, 2003; 36: 35-54.
2. Frilling A, Hertl M. Endemic goiter and benign multinodular goiter. In: Doherty GM, Skogseid B (eds). *Surgical endocrinology*. Philadelphia: Lippincott Williams and Wilkins, 2001, p. 37-45.
3. Studer H, Gebel F. Sporadic goiter in: Ingbar SH, Breverman LE (eds). *Werner's The thyroid, A fundamental and clinical text* 5th edition, Philadelphia; Lippin Cott, 1986, p. 1311-1315.
4. Poulouse KP, Krishna Das KV. Thyroid and its disorders. In: Krishna Das KV, Bahuleyan CG, Haridas K K, Jayakumar PV, Visweswaran K, Krishna Kutty K et al (eds). *Text book of medicine*, 4th edition, New Delhi; Jaypee brothers, 2002, p. 490-501.
5. Hooper M. Thyroid. In: Iain MCA, Leadingham CM (eds). *Jamieson and Kay's Text book of Surgical Physiology* 4th edition, London; Churchill Livingstone, 1988, p. 95-107.
6. Hurley DL, Gharib H. Evaluation and management of multinodular goiter. *Otolaryngol Clin N Am.*, 1996; 29(4): 527-540.
7. Krukowski Z H. The thyroid and the thyroglossal tract. In: Russell RCG, Williams NS, Bulstrode CJK (eds). *Bailey and Love's short practice of surgery* 24th edition. London; Arnold, 2004, p. 776-803.
8. Studer H, Gerber H. Multinodular goiter. In: De Groot CJ, Besser M, Burger HG, Jameson JL, Odell W D, Marshall JC (eds) *Endocrinology*, 3rd edition, Philadelphia: WB Saunders, 1995, p. 769-78/2 (vol 1).
9. Taylor S. The evolution of nodular goiter. *J Clin Endocrinol Rev.*, 1953; 13: 1232-1247.
10. Ljunberg O. Non toxic goiter. In: *Biopsy pathology of the thyroid and parathyroid*, 12th edition, London: Chapman Hall Medical, 1992, p. 75-102.