# **Original Research Article**

DOI: http://dx.doi.org/10.18203/2349-2902.isj20204132

# Multinodular goitre: a clinicopathological study from Kerala

Meena Asokan<sup>1</sup>, Shanavas Cholakkal<sup>2\*</sup>, Bibilash Babu Susheela<sup>3</sup>, Hima Abdurahiman<sup>4</sup>

Received: 15 July 2020 Revised: 19 August 2020 Accepted: 24 August 2020

# \*Correspondence:

Dr. Shanavas Cholakkal,

E-mail: shanavascholakkal@gmail.com

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#### **ABSTRACT**

**Background:** Multinodular goiter (MNG) occurs due to repeated hyperstimulation of thyroid gland due to iodine deficiency, goitrogens, antithyroid drugs and genetic defects. MNG can have different complications which include treacheal compression, retrosternal extension, malignancy and secondary thyrotoxicosis. The aim of the work was to study the clinical features and histopathology of MN in patients admitted for thyroidectomy in surgical wards of a tertiary care hospital in north Kerala.

**Methods:** A prospective hospital based observational study in the patients in surgical wards of a tertiary care hospital in north Kerala from April 2011 to March 2012. The clinical data of patients who are subjected to thyroidectomy for MNG (clinical and fine needle aspiration cytology diagnosis) were included in this study. Patients undergoing completion thyroidectomy for recurrence or malignancy were excluded from this study.

**Results:** MNG is more common in females. Female to male ratio 24:1 Majority are in the age group of 30-50 years (64%) with a mean age of 41 years. 38% (38 cases) had pressure symptoms in the form of dysphagia or dyspnea. Secondary thyrotoxicosis seen in 17% (17 cases). Fine needle aspiration cytology (FNAC) is not an error-proof investigation in MNG. 14% of our patients had malignancy inspite of being reported as benign in FNAC. Among the malignancies papillary carcinoma thyroid was found to be most common accounting for 12% of cases (12/100) followed by follicular carcinoma.

**Conclusions:** FNAC is not an error proof investigation in MNG. Incidental thyroid cancer in MNG is about 14 % with papillary carcinoma thyroid being the commonest.

Keywords: Multinodular goiter, Thyroid, Carcinoma thyroid

# INTRODUCTION

The thyroid gland being an important endocrine gland in the neck plays an important role in the regulation of the basal metabolic rate, stimulates somatic and psychic growth. The term thyroid is derived from Greek, which means shield (thyros-shield, eidos-form). Normal thyroid gland is impalpable. Enlargement of the thyroid gland is the most common manifestation of the thyroid disease and is known as goitre. The enlargement may be either generalized or localized, and toxic or nontoxic. The nontoxic goitre is further divided on etiological basis as endemic goitre and sporadic goitre. The endemic goitre is defined as one where more than 10% of population shows thyroid enlargement. Diseases of thyroid gland especially multinodular goiter (MNG) due to deficiency of iodine are prevalent in India. Nodular goiters are more common in women than in men and the nodularity increases with increasing age. MNG can become malignant even though it is rare.

<sup>&</sup>lt;sup>1</sup>Department of Surgery, Travancore Medical College, Kollam, Kerala, India

<sup>&</sup>lt;sup>2</sup>Department of General Surgery, Aster Malabar Institute of Medical sciences Ltd, Kozhikode, Kerala, India

<sup>&</sup>lt;sup>3</sup>Department of Plastic Surgery, Aster Malabar Institute of Medical sciences Ltd, Kozhikode, Kerala, India

<sup>&</sup>lt;sup>4</sup>Department of Pathology, MES Medical College, Perinthalmanna, Kerala, India

Etiopathogenesis of MNG includes iodine deficiency, dyshormonogenesis, intake of certain drugs and goitrogens, radiation and genetic factors. Iodine deficiency may be due to low iodine content in diet/reduced intestinal absorption.1 Dyshormonogenesis is not a common cause and may be due to defects of iodine trap, organification or coupling, protease enzyme deficiency and synthesis of abnormal iodoproteins. Goitrogens block steps in thyroid hormone synthesis or inhibiting iodine uptake cause a hyperplasic gland with compensated thyroid function. They include drugs like thiocarbamides (antithyriod drugs), chlorpropamide, para-aminosalicylic acid (PAS), amiodarone, glutathiamide, reserpine, phenylbutazone, lithium and sulfonylureas. Foods like vegetables of Brassica family cabbage, soyabean and cassava also contain goitrogens.<sup>2</sup> Cabbage contains thiocyanates which inhibit iodine uptake.3 Previous thyroid irradiation increases the incidence of both benign and malignant nodules in the gland.<sup>4</sup> 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 thyroid stimulating hormone (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. Genetic factors suggested in the development of familial non-toxic MNG include MNG-1 on 14q chromosome.

Taylor proposed the evolution of the nodular goitre in five stages- stage 1: the diffuse enlargement of thyroid gland; stage 2: discrete focal areas of hyperplasia; stage 3: lobules become increasingly hyperplastic and vascular, this stage is typified by disruption and haemorrhage; stage 4: nodules undergo resolution in one or two ways, either a large, lace of colloid fills it and this is found to be free of iodine or mass of new follicles grow to supercede it; and stage 5: the MNG is brought about by continued repetition of the process described above, with the result that most of nodules are inactive and incapable to metabolize iodine but among them are few active foci, which are currently supplying normal body requirement.<sup>5,6</sup>

# Histopathology of MNG

The initial stage of nodular goitre is a simple goitre. With the passage of time due to repeated involution and hyperplasia, multiple nodules appear gradually. These nodules increase with advancing years. The thyroid acini are divided into three types depending upon the stage: resting stage, in which the acini are large, lined by flattened cells and filled with dense homogenous colloid; secretory stage, in which acini are lined by cuboidal epithelium and their colloid does not stain intensely; and response phase, in which acini are lined by columnar cells and contain highly stained vacuolated colloid.

As the simple goitre changes to nodular goitre the histological appearance vary according to the stage:

Stage of hyperplasia, which is due to increased TSH, which is secreted in response to low levels of circulating thyroid hormones. In this stage, the acini are hyperplastic and distorted by ingrowths and invagination of epithelium. The acini are lined by tall columnar cells. The colloid is less in amount. This phase will slowly change into colloid goitre.

Colloid phase, where the gland is a mixture of hyperplasia with colloid acini. The acini are lined by cuboidal cells. The concentration of iodine is less than normal gland. When the supply of iodine increases, the gland undergoes involution. Both hyperplastic and colloid goitre are associated with euthyroidism.

Nodular phase, which is an irreversible stage of a simple goitre and is due to repeated stimulation of the gland. The process of hypertrophy, hyperplasia and involution follow repeatedly. Faulty areas of involution associated with colloid distension will compress the normal glandular tissue. This with newly formed fibrous tissue causes the nodule to become encapsulated. Macroscopically the nodules may be single or multiple. The nodules may be pale yellow pink and opaque in appearance. Dissolution of follicle lead to cyst formation and cyst may contain cholesterol crystals and colloid material. Microscopically nodular goitre appears as colloid goitre. It consists of poorly defined fibrous capsule containing colloid filled acini, which are lined by low cuboidal epithelial cells.

#### Retrosternal goiter

Most retrosternal goitres arise from lower pole of a nodular goitre. Very few retrosternal goitre arise from ectopic thyroid tissue. If the neck is short and pretracheal muscles are strong in men, negative intrathoracic pressure tends to draw these nodules into superior mediastinum. A retrosternal goitre is often symptomless and is discovered on a routine chest radiograph. It receives its blood supply from inferior thyroid vessels. Retrosternal goitre may be substernal, intrathoracic, plunging type based on the location of the goitre. A retrosternal goitre however can cause severe symptoms like dyspnoea (particularly at night with cough and stridor, due to pressure on trachea), dysphagia (due to pressure on oesophagus), enlargement of veins on neck and front of chest (due to pressure on great veins at thoracic inlet) or superior vena cava obstruction. A retrosternal goitre may be toxic or malignant. A chest radiograph in case of retrosternal goitre shows widened soft tissue shadow in superior mediastinum sometimes with calcification and often causing deviation and compression of trachea.

# Complications of MNG

Complications of MNG include secondary thyrotoxicosis, tracheal compression and malignant change.

#### Secondary thyrotoxicosis

Its incidence is difficult to estimate but figures as high as 30% are reported. In many cases of toxic nodular goitre the nodules are inactive and it is the internodular tissue that is over active and is due to a family of IgG immunoglobulins which bind with TSH receptor sites (TRABS) and activates TSH receptors on follicular cell membrane. They have a more protracted action than TSH (16-24 hours versus 1.5 to 3 hours). However in some toxic nodular goitre one or more nodules are overactive and here the hyperthyroidism is due to autonomous thyroid tissue as in toxic adenoma and is termed as plummer's disease.

#### Tracheal compression

It may be due to gross displacement of trachea in lateral or anteroposterior plane. It is commonly due to haemorrhage into a nodule and in retrosternal goitre.

### Malignant change

It is one of the most controversial subject which is still not settled. It is an uncommon complication. The incidence of carcinoma in MNG has been reported as 5-10%. In this view Sokal has reported that 4% to 17% of nodular goitre develop thyroid cancer. The malignancy is usually of papillary carcinoma. Aim of the work was to study the clinical features and histopathology of MNG in patients admitted for thyroidectomy in surgical wards and to find out the percentage of incidental thyroid malignancy in the MNG in the population of Kerala. We also examined the concomitant incidence of toxicity and malignancy in MNG.

#### **METHODS**

We conducted a prospective cross sectional study in the patients in surgical wards of a tertiary care hospital at north Kerala from April 2011 to March 2012.

Sample size required was calculated using the formula

$$n = 4pq/l^2$$

where  $\boldsymbol{l}$  is the margin of error, taken as 5% or 0.05,  $\boldsymbol{p}$  is the prevalence of MNG=4% or 0.04, and  $\boldsymbol{q}$  is  $\boldsymbol{1}-\boldsymbol{p}$ .

Minimum sample size required was 64. Hence a total of 100 patients were enrolled in to this study.

#### Inclusion criteria

All the patients who are admitted to the hospital Surgical ward and subjected to thyroidectomy for MNG (clinical or FNAC diagnosis) were included in this study.

#### Exclusion criteria

Patients with solitary thyroid nodule and undergoing completion thyroidectomy for recurrence or malignancy were excluded from this study.

#### Ethical approval

Institutional ethics committee approval was obtained prior to the starting of the study and informed written consent from the participants were obtained prior to enrolment in to the study.

#### Methodology

Clinical data of patients admitted with MNG for thyroidectomy was analyzed. A detailed history was taken and thorough clinical examination done along with histopathology follow-up which was entered in the proforma. Biochemical evaluation of T3, T4 and TSH was done in all patients prior to surgery to rule out toxicity. Retrosternal extension was found out through x-ray, clinical examination and/or computed tomography (CT) scan. All the data collected were entered in to masterchart and statistical analysis was done using Statistical Package for the Social Sciences (SPSS) version 18.0.

## **RESULTS**

A total of 100 patients were included in this study. The age of our patients varied from 15 to 80 years (mean age-41 years). 33% (33 patients) were in the age group of 31-40 years while 31% (31 patients) were in the age group of 41-50 years. So a total of 64% of our patients were between 30-50 years of age (Table 1). Most (96%) of our patients were females and ratio of female to male patients was 24:1. This clearly demonstrates that females are at a higher risk of developing MNG compared to males. It may also be noted in the age group of 11-20 and 21-30 years we did not have male patients while all of these were females. This indicates that probably the disease process starts early in the females compared to the males.

Table 1: Age and sex wise incidence of MNG.

Age (in years)	Male	Female	Total	Percentage
0-10	00	00	00	00
11-20	00	01	01	01
21-30	00	19	19	19
31-40	02	31	33	33
41-50	02	29	31	31
51-60	00	12	12	12
≥61	00	04	04	04
Total	04	96	100	100

#### Clinical features

Most of our patients had involvement of both the lobes (88%), while rest (12%) had involvement of one lobe (right-7%, left lobe-5%, isthmus-0%). All (100%) of our patients presented with swelling in front of the neck. 94% of our patients had painless swelling, while 6% had pain (Figure 1). Pressure symptoms (dyspnoea and dysphagia)

were noticed in 38 %, while 62% did not show any pressure symptoms (Figure 2).

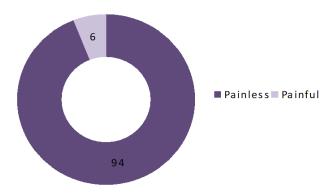


Figure 1: Incidence of pain in MNG.



Figure 2: Incidence of pressure symptoms.

## Incidence of toxicity

17% of our patients had toxic MNG, while 83% had non-toxic MNG. Male had slightly increased (25 % versus

16%) incidence of toxicity as compared to females, but this difference was not statistically significant (p-value=0.663758) (Figure 3).

#### Retrosternal extension

Retrosternal extension was noticed only in 5 % of the cases (Table 2). Retrosternal extension was noticed in clinical examination and was further confirmed with chest x-ray.

Table 2: Retrosternal extension.

Lower border	Total no. of cases	Percentage	
Lower border not seen	5	5	
Lower border seen	95	95	
Total	100	100	

#### Type of surgery done

Total and near total thyroidectomy was done in most of the cases (69%). While subtotal thyroidectomy was done in 19%, rest of the patients underwent hemithyroidectomy (12%). In the patients, who had underwent hemithyroidectomy, MNG was restricted to the single lobe (Table 3).

Table 3: Type of surgery done in MNG.

Туре	Total number	Percentage
Hemi thyroidectomy	12	12
Subtotal thyroidectomy	19	19
Near total thyroidectomy	34	34
Total thyroidectomy	35	35
Total	100	100

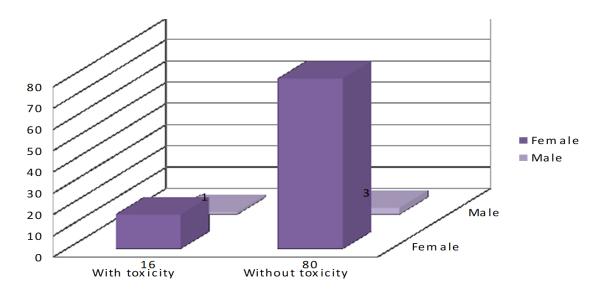


Figure 3: Incidence of toxicity in MNG.

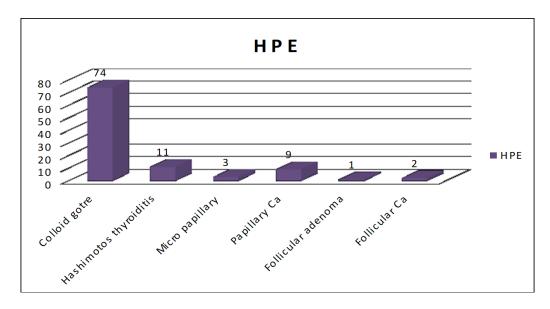


Figure 4: HPE of thyroidectomy specimen.

#### Histopathology of thyroidectomy specimen

Most of the thyroidectomy specimen was reported as colloid goitre (74%). Hashimotos thyroiditis was reported in 11%. Follicular adenoma was reported in 1%. Differentiated thyroid cancer was reported in 14% (papillary carcinoma 9%, 3% papillary microcarcinoma, 2% follicular carcinoma) (Table 4).

## Concomitant incidence of toxicity with malignancy

We also evaluated the incidence of malignancy in toxic MNG. Our study did not show any concomitant incidence of malignancy with toxicity in MNG.

Table 4: Histopathology of thyroidectomy specimen.

HPE report	Total no. of cases	%
Colloid goitre	74	74
Hashimoto's thyroiditis	11	11
Micro papillary carcinoma	3	3
Papillary carcinoma	9	9
Follicular adenoma	1	1
Follicular carcinoma	2	2
Total	100	100

## **DISCUSSION**

We studied a total of 100 patients- 4 were males and 96 were females - with a female to male ratio of 24:1. Rios et al showed that 89% of patients with MNG were females. <sup>12</sup> In the study conducted at King George Hospital in Vishakapatnam, female to male ratio was 5:1. <sup>13</sup> Our study also suggest MNG is more common in females (female to male ratio 24:1) majority are in the age group of 30-50 years (64%). Table 1 shows the age and sex distribution of the patients studied. Majority of the females 33%, (33

cases) presented in the age group between 31-40 years. In the western literature quoted by "Bremer and Moll Night" after analysis of 1280 cases of MNG, the age incidence was found to be maximum between 40-49 years. Hence the average age incidence in our study is the same compared to western series. In our study maximum age of presentation was 74 years and minimum age was 20 years with an average age incidence of 41 years. It may also be noted in the age group of 11-20 and 21-30 years we did not have male patients while all of these were females. This indicates that probably the disease process starts early in the females compared to the males.

The chief complaint in majority of the patients (100%) is swelling in front of the neck. Out of 100 cases, 6% (6 cases) had associated pain in the neck and 38% (38 cases) have pressure symptoms in the form of dysphagia or dyspnea. Pressure symptoms were seen in 38% (38 cases) as against 29% in Rios et al study. Secondary thyrotoxicosis is seen in 17% (17 cases). Toxic symptoms were seen in 49% of cases in Rios et al study. The clinical features of the nodule were not helpful in the diagnosis of malignancy. There was no correlation between the consistency, duration and size of the nodules and malignancy.

Types of surgeries performed and its details are given in Table 3, of different procedures, total thyroidectomy (35%) and near total thyroidectomy (34%) were the most commonly performed ones.

FNAC is very useful in the diagnosis and management of MNG. Malignancy can still come as a surprise on post-operative histopathological examination, even when there is no suspicion of malignancy clinically and with FNAC. 11,14,15 FNAC of the thyroid was done in all the cases and the results compared with histopathological report of operated specimen. 3 cases of micro papillary carcinoma (less than 1 cm) were pre operatively diagnosed

as colloid goitre. This shows that FNAC is not 100% accurate in the diagnosis of micro papillary carcinoma. Among the malignancies papillary carcinoma thyroid was found to be most common accounting for 12% of cases (12/100) followed by follicular carcinoma.

# Relationship between thyroiditis and malignancy

Hashimotos thyroiditis was reported in 11% of patients underwent thyroidectomy. It is important to note that 54% (6 patients) our patients with thyroiditis had neck pain. Hence authors suggest routine investigation with antithyroid antibodies in the patients with MNG having neck pain. Our study did not show any concomitant incidence of thyroiditis with maliganancy, however the present literature suggests the incidence of malignancy in thyroiditis. 16,17 In a meta-analysis conducted by Lai, the mean rate of papillary thyroid cancer among patients with Hashimoto's thyroiditis ranged from 1.12% to 40.11% and Hashimoto's thyroiditis patients had an increased risk (OR=2.12) of developing malignancy compared to normal individuals. However since we had only 11 patients with histopathology reported as Hashimoto's thyroiditis, authors are in a view that further prospective studies are required before coming in to a conclusion.

#### Concomitant incidence of toxicity with malignancy

We also evaluated the incidence of malignancy in toxic MNG. Out of 17 patients with toxic MNG, none was reported to have malignancy in the final histopathology report. However, in the study conducted by Pacini, after reviewing 179 patients who underwent thyroidectomy for thyrotoxicosis, 7.5 % patients with toxic MNG had malignancy. Similar study was also conducted by Preece et al in 2014. Hence authors suggest the need for further prospective studies before coming in to a conclusion.

#### **CONCLUSION**

MNG is more common in females. Female to male ratio 24:1, majority are in the age group of 30-50 years (64%) with a mean age of 41 years. The chief complaint in majority of the patients (100%) is swelling in front of the neck. 6% (6 cases) have pain in the neck. 38% (38 cases) had pressure symptoms in the form of dysphagia or dyspnea. Secondary thyrotoxicosis seen in 17% (17 cases).

FNAC is not an error-proof investigation in MNG. 14 % of our patients had malignancy inspite of being reported as benign in FNAC. Among the malignancies papillary carcinoma thyroid was found to be most common accounting for 12% of cases (12/100) followed by follicular carcinoma.

#### Limitations

Our study was limited to the clinicopatholgical correlation of MNG. We did not include early and late postoperative complications in this study.

Funding: No funding sources Conflict of interest: None declared

Ethical approval: The study was approved by the

Institutional Ethics Committee

#### REFERENCES

- 1. Krohn K, Führer D, Bayer Y, Eszlinger M, Brauer V, Neumann S, et al. Molecular pathogenesis of euthyroid and toxic multinodular goiter. Endocr Rev. 2005;26(4):504-24.
- 2. Ekpechi OL, Dimitriadou A, Fraser R. Goitrogenic activity of cassava (a staple Nigerian food). Nature. 1966;210(5041):1137-8.
- 3. Langer P. Study of chemical representatives of the goitrogenic activity of raw cabbage. Physiol Bohemoslov. 1964;13:542-9.
- Pacini F, Vorontsova T, Demidchik EP, Molinaro E, Agate L, Romei C. Post-chernobyl thyroid carcinoma in belarus children and adolescents: comparison with naturally occurring thyroid carcinoma in Italy and France. J Clin Endocrinol Metab. 1997;82(11):3563-9.
- 5. Taylor S. The evolution of nodular goiter. J Clin Endocrinol Metab. 1953;13(10):1232-47.
- 6. Taylor S. Physiologic considerations in the genesis and management of nodular goiter. Am J Med. 1956;20(5):698-709.
- 7. Kimpkin H. Thyroid Chapter 37, 8th edition. 1970;1065-89.
- 8. Ramzi CS. The endocrine system thyroid gland; Chapter 25, Robins pathological bases of disease, 5th edition WB Saunders Company; 1994:1121-1142.
- 9. Sokal JE. Incidence of malignancy in toxic and nontoxic nodular goitre. JAMA. 1954;154:1321-5.
- 10. Sokal JE. The problem of malignancy in nodular goiter. JAMA. 1959;170:405.
- 11. Pelizzo MR, Piotto A, Rubello D, Casara D, Fassina A, Busnardo B. High prevalence of occult papillary thyroid carcinoma in a surgical series for benign thyroid disease. Tumor. 1990;76(3):255-7.
- 12. Zambudio AR, Rodríguez J, Riquelme J, Soria T, Canteras M, Parrilla P. Prospective study of postoperative complications after total thyroidectomy for multinodular goiters by surgeons with experience in endocrine surgery. Ann Surg. 2004;240(1):18-25.
- 13. Kodi S, Waddi S, Katakam SK. A prospective study on toxic multinodular goitre in surgical wards of Andhra medical college, Visakhapatnam. J Evid Based Med Heal. 2016;3(51):2349-562.
- 14. Rios A, Rodriguez JM, Galindo PJ, Montoya M, Tebar FJ, Sola J, et al. Utility of fine-needle aspiration for diagnosis of carcinoma associated with multinodular goitre. Clin Endocrinol (Oxf). 2004;61(6):732-7.
- 15. Koh KBH, Chang KW. Carcinoma in multinodular goitre. Br J Surg.1992;79(3):266-7.
- 16. Singh B, Shaha AR, Trivedi H, Carew JF, Poluri A, Shah JP. Coexistent Hashimoto's thyroiditis with

- papillary thyroid carcinoma: impact on presentation, management, and outcome. Surgery. 1999;126(6):1076-7.
- 17. Jayaprakash K, Kishanprasad H, Hegde P, Chandrika R. Hashimotos Thyroiditis with coexistent papillary carcinoma and non-Hodgkin lymphoma-thyroid. Ann Med Health Sci Res. 2014;4(2):268-70.
- 18. Pacini F, Elisei R, Di Coscio GC, Anelli S, Macchia E, Concetti R, et al. Thyroid carcinoma in thyrotoxic

patients treated by surgery. J Endocrinol Invest. 1988;11(2):107-12.

Cite this article as: Asokan M, Cholakkal S, Susheela BB, Abdurahiman H. Multinodular goitre – a clinicopathological study from Kerala. Int Surg J 2020;7:3333-9.