REVIEW ARTICLE

Medullary Thyroid Carcinoma and Calcitonin –A Critical Review

SM Khorshed Alam Mazumder[1], Daulatuzzaman[2], Khandaker Ezaz Ahmed[3]

Introduction :

Medullary carcinoma arises from the parafollicular C cells of the thyroid which are neuroectodermal in origin.Hence it may be associated with other tumours of neuroectodermal origin as in MEN IIa and MEN IIb.Most medullary carcinomas are located in the middle and upper thirds of the thyroid lobes which are derived from the ultimobranchial bodies having C cells.

It is the third most common of all thyroid cancers (about 5-8%) .Medullary carcinoma can be sporadic (more common) or familial.The latter may be associated with MEN type IIA and IIB or without any endocrinopathy.parafollicullar cells secrete calcitonin and a carcinoembyonic antigen .Levels calcitonin have been used in the diagnosis of medullary carcinoma and in postsurgical follow up for recurrent or residual tumours.

Physiology: Calcitonin is secreted by the parafollicular c. cells of the thyroid gland .Calcitonin participates in calcium and phosphours metabolism . Most evidence indicates that calcitonin is of very little physiological importance to humans . Its primary physiological effects is to lower serum calcium levels . It does this , in part , by inhibiting bone resorption and by promoting urinary clearance of calcium[3].various forms of Calcitonin (CT) may be detected in blood samples ,including a CT monomer ,an oxidized monomer , a dimmer , higher moleculer weight forms and possibly precursor of CT. The concentrations of these peptide vary with clinical status, renal function and tissular origin of CT[4]. Rather, calcium and phosphates homeostasis is primary under the control of parathyroid hormone (PTH). Calcitonin reduces blood calcium levels in three ways: decreasing calcium absorption by the intestines, decreasing osteoclast activity in bones, decreasing calcium and phosphates resorption by the kidney tubules.

1) Professor & Head ,Department of ENT - Head & Neck Surgery, Holy Family Red Crescent Medical College Hospita, Dhaka

2) Professor Department of ENT - Head & Neck Surgery, Holy Family Red Crescent Medical College & Hospital .Eskaton,Dhaka

3) Professor & Head, Department of anesthesiology Holy Family Red Crescent Medical College Hospital, Dhaka.

History : Medullary thyroid cancer was first described by Harzard et al in 1959.The recognition of calcitonin as a calcium lowering hormone in 1962 and its origin from the thyroid parafollicular cells ,so named by Nonidez 1932 ,was resported by foster et al .pearse and polak adopted the term C cells and first described their origin from neural crest tissue.

Calcitonin was not recognized as a specific hormone until 1962.Calcitonin was purified in 1962 by copp and cheney , While it was initially considered a secretion of parathyroid glands . it was later identified as the secretion of the C-cells (parafofficular cells) of the thyroid [5].

Medullary Carcinoma of the Thyroid

Medullaru thyroid carcinoma ia a tumor of parafollicular C-cells derived from nrural crest . Familial association has been detected in many occasions . Approximately 75% of medullary carcinoma occusrs as a non –inherited , sporadic lesion , presenting typically in the fourth decade as a unifocal lesion without associated endocrinopathy . Inherited MTC accounts for the remaining 25% and may occur in three discrete inherited forms . MEN IIa , MEN IIb , and familial MTC (FMTC)[6,1]. All inherited forms of MTC are autosomal dominant . Involvement of lymph nodes occur in 50-60 percent of cases of medullary carcinoma and blood borne metastasis are common .The RET proto – oncogene plays a role in the development of inherited forms of MTC and has become important in the clinical management of patient s and their families . It is due to the multifocal nature of inherited disease ,total thyroidectomy is the minimum surgical recommendation for all forms of medullary thyroid cancer[7]. As would be expected , tumors are not hormone dependent and do not take up radioactive iodine . Recent works has suggested that in patients with palpable disease bilateral neck dissection are important in controlling regional nodal micrometastasis.

Calcitonin:

Serum calcitonin (CT) is a sensitive and accurate marker of MTC; an elevated basal calcitonin level confirms the cytological or histological diagnosis of MTC in a symptomatic patient . False-positive serum calcitonin levels are recorded

in patients with autoimmune thyroid diseases,hypercalacaemia,foregut-derived neuroendocrine tumours ,and renal failure .Conversely MTC cases with normal basal serum calcitonin are recogniged.Measurement of Calcitonin is the most reliable method for diagnosis of Medullary Thyroid Carcinoma (MTC) , C-cell Neoplasia) . MTC in the inherited familial form may exist in association with pheochromocytoma and parathyroid diseases (Multiple endocrine Neoplasia Syndrome 11 or MEN 11), multiple mucosa neuromas intestinal ganglioneruomatosis, marfanoid habitus and other abnormalities[8,3]. These conditions, therefore should be kept in picture while dealing with elevated Calcitonin levels. Calcitonin ia a 32 amino acid polypeptide hormone secreted by parafollicular C cells , which acts to depress serum calcium levels by inhibiting osteoclastic activity and increasing calcium renal excretion[9]. Physiologic importance of calcitonin, however, is considered to be slight. Total thyroidectomy is not associated with increased calcium levels. Calcitonin does promote intestinal secretion of water and electrolytes. Extreme calcitonin elevations in patients with widely metastatic diseases have been associated with chronic and severe diarrhoea[10]. Calcitonin elevation occurs in C-cell hyperplasia and all forms of MTC . However , patients with C-cell hyperplasia or early MTC may have normal basal calcitonin levels .

Generally, basal calcitonin levels roughly correlate with tumors burden .patients with palpable diseases may have levels greater than 1,000 pg/ml . while patients metastatic diseases may have levels greater than 1000,000 pg/ml . The infusion of calcium and / or pentagastrin can elevate basal calcitonin levels in patients with C- cell hyperplasia and frank MTC [11]. pentagastrin is believed to be the most efficient agent for provocative calcitonin stimulation . provocative testing is considered to be positive when calcitonin levels are elevated to twice the basal level, of gene carries of inherited diseases ,95% will convert to a positive calcitonin test by 35 years of age , with the average age of conversion being 13 years of age [12-18].

Interpretation :

Basal calcitonin levels are elevated in only approximately two thirds of patients who present with MTC [2,3,4].

Normal reference range : Males :0.0-18.2 Pg/ml. Female: 0.0-11.5pg/ml.

1 Raised in C- cell hyperplasia and MTC and other pathological conditions .

2 100 pg /ml May found in pathological conditions like leukemias and other myeloproliferative disorders .

3 1000 pg /ml : Palpable MTC without metastasis.

4 10000 pg /ml : Metastatic MTC .
Provocative test with calcium and /or

Pentagastrin:

5 Provocative testing in considered to be positive when calcitonin levels are elevated to twice the basal level .

6 Pentagastrin
105pg/ml in women

210pg /ml in men

Indicates MTC or C-cell hyperplasia (C-CH)

Calcium

120pg /ml in women

265 pg/ml in Men s

Indicates MTC or C-cell hyperplasia (C-CH)

Combined test :> 300 pg/ml

Indicates MTC or C-cell hyperplasia (C-CH)

Other pathological situation : Unresponsive to provocative test

Conclusion:

As a tumor Marker , thus Serum calcitonin measurements are useful in diagnosis ,to see severity of diseases,testing effectiveness of surgery ,post operative follow up for recurrence and for diagnosis of preclinical MTC (provocation with calcium or pentagastrin) ,and other calcitonin producing tumours and differentiation.Calcitonin measuring facilities should be available all over the country to facilitate proper management of MTC .

References :

1. Block MA , Jackson CE , Greenawald KA , et al . clinical charac – teristics distinguishing heareditary form sporadic medullary thyroid carcinoma ,Arch Surg.1980;115:142-148.

2. Deftos u.Radioimmunoassay for calcitonin in medullary thyroid carcinoma. JAMA 1974; 227: 403.

3. Favus(ed) . primer on the metabolic bone diseases and disorders of mineral metabolism , 2nd ed .1993;97.

4. Gregory w. Randolph , and Dipti Maniar : Medullary Carcinoma of the Thyroid, Cancer control May /june 2000; 7 (3) :253-261

5. Austin L and Heath H. Calcitonin: physiology and pathophysiotogy. N Engl J Med 198; 304: 269-278.

6. Chong GC, Beahrs OH, Sizemore GW, et al. Medullary carcinoma of the thyroid gland. Cancer, 1 975; 35: 695-704.

7. Saad MF, Ordonez NG, Rashid RK, et al. Medullary carcinoma of the thyroid: a study of the clinical features and prognoitic factors in 161 patients. Medicine. .1984; 63: 319-342.

8. Bergholm U. Adami HO, Bergstrom R, et al. Clinical characteristics in sporidic and familial medullary thyroid carcinoma: a nationwide study of 249 patients in Sweden from 1989 through 1 981. Cancer. 1 989; 63: 1196-1204.

9. Samaan NA,Schultz Hickey RC. Medullary carcinoma of the thyroid: differentiating the types and current management. Oncology (Huntingt). 1987; 1 : 21- 28.

10. Samaan NA, Schultz pN, Hickey RC. Medullary thyroid carcinoma: prognosis of familial versus sporadic disease and the role of radiotherapy. J Clin Endocrinol Metab. 1988; 67: 801-805.

11. Fleming JB, Lee JE, Bouvert M, et aL Surgical strategy for the treatment of medultary thliroid carcinoma. Ann Surg. 1999; 230: 697.

12. Hoefnagal CA, Delprat CC. Valdes Olmos RA. Role of (131 l) metaiodobenzylguanidine therapy in medullary thyroid carcinoma.

13. Bergholm U, Bergstrom R, Ekbom A. Long-term follow-up of patients with medullary carcinoma of the thyroid. Cancer. 1997; 79:132-138.

14. Brunt LM, Wells SAJr. Advances in the diagnosis and treatment of medullary thyroid carcinoma. Surg CIin North Am. 1987;67:263-279.

15. Rougier p, parmentier C, Laplanche A, et al. Medullary thyroidcarcinoma: prognostic factors in treatment. Int J Radiat Oncol Biot phys 1983; 9:161-169.

16. Brierley J, Tsang R, Simpson WJ, et al. Medullary thyroid cancer: analyses of survival and prognostic factors and the role of radiation therapy in local control. Thyroid. 1996; 6: 305-310.

17. Moey JF, Wells SA, Dilley WG. Reoperation for recurrent or persistent medullary thyroid cancer. Surgery. 1 993; 114: 1090-1096.

18. Moley JF, DeBenedetti MK, Diltey WG, et al. Surgical Management of patients with persistent or recurrent medullary thyroid cancer. J lntern Med. 1998;243: 521-526.