

Association of calcium-stimulated calcitonin values with pathological findings following total thyroidectomy

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Background and Objectives: Medullary Thyroid Carcinoma (MTC) is a rare neuroendocrine tumor arising from the parafollicular or C cells of the thyroid and it usually secretes calcitonin (CT), in large amounts. MTC accounts for 3 – 4% of all thyroid malignancies [1]. It is inherited in 20 – 30% of cases where it develops in the setting of MEN 2, induced by germline mutations in Rearranged during Transfection (RET) proto-oncogene [2]. Prognosis of MTC is not as favorable as that of other forms of Differentiated Thyroid Carcinoma of follicular origin (DTCf), i.e. Papillary Thyroid Carcinoma (PTC) and Follicular Carcinoma (FTC).

Measurement of basal CT level (bCT) and calcium (or pentagastrin) peak stimulated CT level (psCT) is used in the last decades for an earlier diagnosis, since treatment in less advanced stages is expected to forestall regional or distant metastasis and increase likelihood of radical cure [3]. Based on several studies, it is generally agreed that bCT > 10 pg/ml necessitates the performance of a CT stimulation test and bCT or psCT > 100 pg/ml are an indication for total thyroidectomy [4]. However, CT levels may be elevated in patients with C-cell Hyperplasia (CCH) and in this case thyroidectomy might prove unjustified. CCH shows overlapping bCT and psCT values with MTC and various respective cut-off points have been proposed by a large number of studies in an attempt to preoperatively differentiate MTC from CCH. The objective of this study was to investigate the utility of calcium stimulation test for CT in order to distinguish MTC from CCH preoperatively and to examine the histological findings of thyroidectomy in patients with peak stimulated CT >100 pg/ml.

Patients and Methods: A total of 55 patients with thyroid nodules and basal CT levels between 6 and 100 ng/l had a positive calcium stimulation test (peak CT >100 ng/l) and underwent total thyroidectomy. Their mean age (\pm SD) was 54.9 \pm 13.6 years (range 15-76), 58.7 \pm 11.0 for men (range 37-76) and 50.9 \pm 15.1 for women (range 15-75). Secondary causes of hypercalcitoninemia (proton pump inhibitor therapy, renal failure, hepatic cirrhosis, atrophic gastritis, hypercalcemia and hypergastrinemia) were ruled out. The calcium stimulation test was performed with the intravenous injection of calcium gluconate in 3 minutes at a dose of 2.3 mg/kg of elemental calcium. Blood samples were collected at 0, 1, 2, 3 and 5 minutes after the injection. The only adverse effects were occasional brief (<1 min) bouts of nausea, headache, and/or flushing.

Results: Based on surgical histology, 20 patients (36%) harbored a MTC, 12 women (60%) and 8 men (40%). MTC was multifocal in 6 patients and a single focus in the remaining 14. Mean longest tumor diameter was 6.1 \pm 2.9 mm (median 7mm, range 0.5-11 mm) with only 3 tumors \geq 10 mm. Among MTC patients 6 (30%), 3 men, had a coexistent DTCf, 5 papillary and 1 follicular thyroid carcinoma. All the 6 DTCf tumors were at a distance from MTC.

The remaining 35 patients (64%) had CCH, mostly diffuse and/or focal and occasionally nodular (6 patients). Among CCH patients, 14 (40%) had a coexistent PTC. In total, 20 patients (36%) had DTCf, 12 with a solitary focus (60%), 7 PTCs and 1 FTC and 8 (40%) with multifocal PTC. All DTCfs were microcarcinomas with mean longest diameter 2.9 \pm 2.3 mm (median 2.0, range 0.3-9 mm).

Out of 20 patients with MTC, 12 agreed to perform RET gene analysis and 7 were diagnosed as Multiple Endocrine Neoplasia (MEN) Type 2A with 6 patients harboring the G533C mutation in RET exon 8, a frequent mutation in our country [5] and 1 patient with the mutation C634R in exon 11. Among the 7 MEN2A patients, one patient with the G533C mutation had a coexistent PTC.

In ROC curve the best cut-off point of bCT that differentiated MTC patients from CCH patients was 17.4 pg/ml, sensitivity 80%, specificity 63%, (AUC 0.80, P < 0.001, CI 0.68-0.92), with positive predictive value (PPV) 55% and NPV 85%. The best cut-off for psCT was found at 452 pg/ml with sensitivity 85%, specificity 86%, (AUC 0.88, P < 0.001, CI 0.77-0.98), PPV 59% and NPV 79%. Lastly, for the Δ CT value ROC curve gave as the best cut-off the 412 pg/ml, sensitivity 85%, specificity 86% (AUC 0.87, P < 0.001, CI 0.77-0.98), PPV 59% and NPV 79%.

Conclusion: A large percentage of MTC may be identified by peak stimulated CT levels >100 pg/ml preoperatively, but overlapping calcitonin levels between MTC and CCH reduce the accuracy of the test. Remarkably, many patients with peak stimulated CT levels >100 pg/ml harbor a DTCf. A probable association between C-cell disease and DTCf needs further examination.

References

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