Clinical THYROIDOLOGY
AMERICAN THYROID ASSOCIATION FOUNDED 1923

A Conservative Approach Based on Measurement of Calcitonin Permits Delay in Surgical Treatment of RET Mutation–Positive Medullary Carcinoma

Elisei R, Romei, C, Renzini G, Bottici V, Cosci B, Molinaro E, Agate L, Cappagli V, Miccoli P, Berti P, Faviana P, Ugolini C, Basolo F, Vitti P, Pinchera A. The timing of total thyroidectomy in RET gene mutation carriers could be personalized and safely planned on the basis of serum calcitonin: 18 years experience at one single center. J Clin Endocrinol Metab 2012;97:426-35.

SUMMARY

Background

Medullary thyroid cancer (MTC) can occur as part of three different syndromes—MEN2A, MEN2B, and familial medullary cancer (FMTC). A delay of the diagnosis until lymph-node metastases and local infiltration are present has dramatic consequences, including a high death rate. Early diagnosis is therefore mandatory. In 1993, a marker for the germline mutation of RET proto-oncogene was discovered and, as a consequence, genetic screening of families with cases of medullary thyroid cancer with or without hyperparathyroidism and/or pheochromocytoma was rapidly accepted as a standard procedure. In patients carrying the mutation (gene carriers, GC), early prophylactic thyroidectomy was recommended. In 2009, the ATA published guidelines using a staging system to define different risk levels (1). Early operation remained the treatment of choice. The present prospective study from a large center in Italy proposed that the indications for thyroidectomy be modified, taking into account in GC patients basal and pentagastrin (PG)-stimulated serum calcitonin levels.

Methods and Results

During an observation period of 18 years, 103 MTC families were followed (28 MEN2A, 8 MEN2B, and 67 FMTC); 472 subjects were investigated. Screening of all families revealed 140 subjects with germline mutations (for the individual mutations, see the original text); 89 subjects had already been diagnosed and had undergone thyroidectomy before entering the study, and 84 subjects agreed to participate in the study.

Three groups were formed. In group I, the worst cases, basal calcitonin levels were increased and the PG test was pathological. In these subjects neck ultrasound revealed suspicious tissue in 20 of 21 cases. In group II, basal calcitonin levels were normal (<10 pg/ml) but PG tests were positive. Included in this group are patients whose initial PG tests were negative but became positive several years later (mean, 4 years). Group III had both normal basal and PG tests. Nevertheless, even in this group, neck ultrasonography revealed some abnormal tissue in approximately 30% of cases (no details are given). Interestingly, there was no correlation between the classification according to the calcitonin levels and the criteria of severity according to the guidelines of the American Thyroid Association.

Of the GC patients, 53 underwent total thyroidectomy with central-lymph-node neck dissection. Of particular interest was the finding that the value of 60 pg/ml of calcitonin was a highly specific and sensitive indicator of lymph-node involvement, which is a most critical prognostic factor. In patients with calcitonin levels between 10 and 60 pg/ml, MTCs at operation were small and confined to the thyroid. In group II, with calcitonin levels of 10 pg/ml or less but a pathological PG test, the tumors were small (maximum, 0.7 cm in diameter), with no lymph-node involvement. In four initially negative cases that became positive within 4 years, the tumors were between 0.1 and 0.3 cm. The remaining subjects with normal calcitonin levels did not show evidence of MTC at follow-up and are currently still under annual control. Thus, particularly in patients below 16 years of age, thyroidectomy could be delayed without compromising the prognosis.

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Conclusions

The study shows that in GC patients, an alternative strategy to the initial thyroidectomy can be safely adopted by using basal and PG-stimulated calcitonin levels as criteria; in countries where PG is not available, this test can be replaced by calcium gluconate infusions (2, 3). A basal value of calcitonin of 60 pg/ml or more indicates significant disease necessitating intervention. In contrast, if calcitonin levels are 10 pg/ml or less, tumor involvement is minimal. Another group has put the critical level at 30 pg/ml (4). Obviously, patients need an annual complete clinical evaluation. Thanks to this strategy, surgery can be delayed, which is particularly beneficial in young patients. In none of these GC cases was there rapid evolution from minimal disease to a severely progressive disease.

ANALYSIS AND COMMEMTARY

The screening of families of GC patients usually leads rapidly to early thyroidectomy in affected patients. Very often, thyroidectomies are performed in children as young as 5 years of age. Surgery in such young children is not without risks. To meet concerns, the guidelines of the ATA propose a more differentiated approach. The present study describes probably the most conservative approach proposed so far. It is certainly appreciated by the parents and the children carrying this disease. There are some minor caveats. At present, the number of patients studied is still small and one has to be aware of possible GC carriers that progress rapidly from a stage of normal basal and stimulated calcitonin levels to severe disease. In the present study the 4 cases that evolved in this way, had only minimal cancers at operation, which is so far reassuring. Another caveat are those patients who were lost to follow-up. Probably the clinician will feel safer if the patient had thyroidectomy before being lost to follow-up. Finally, in group III, with no pathological basal and stimulated calcitonin levels, neck ultrasound revealed pathological structures in one third of all subjects. Unfortunately, the authors give no further information about this disturbing observation. The reader is left to conclude that the finding was interpreted as being totally different from anything resembling MTC. If not so, the whole message of the article would have to be put into question.

— Albert G. Burger, MD

REFERENCES

1. Kloos RT, Eng C, Evans DB, Francis GL, Gagel RF, Gharib H, Moley JF, Pacini F, Ringel MD, Schlumberger M, et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. Thyroid 2009;19:565-612.
2. Elisei R, Pinchera A. Advances in the follow-up of differentiated or medullary thyroid cancer. Nat Rev Endocrinol. April 3, 2012 [Epub ahead of print]. doi: 10.1038/nrendo.2012.38.
3. Colombo C, Verga U, Mian C, Ferrero S, Perrino M, Vicentini L, Dazzi D, Opocher G, Pelizzo MR, Beck-Peccoz P, Fugazzola L. Comparison of calcium and pentagastrin tests for the diagnosis and follow-up of medullary thyroid cancer. J Clin Endocrinol Metab 2012;97:905-13. Epub December 14, 2011.
4. Rohmer V, Vidal-Trecan G, Bourdelot A, Niccoli P, Murat A, Wemeau JL, Borson-Chazot F, Schvartz C, Tabarin A, Chabre O, et al. Prognostic factors of disease-free survival after thyroidectomy in 170 young patients with a RET germline mutation: a multicenter study of the Groupe Francais d'Etude des Tumeurs Endocrines. J Clin Endocrinol Metab 2011;96:E509-18. Epub December 29, 2010.