Medullary thyroid carcinoma. Genetic screening and prophylactic thyroidectomies

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Medullary thyroid cancer is a rare, neuroendocrine, tumor. It arises from parafollicular or C-cells with the ability to produce and secrete different bioactive substances like calcitonin (TC) and CEA (1-5) TC is ideal tumor marker in early diagnosis, in patients' follow up and in evaluation of their treatment. TC determinations after ca/pentagastrine stimulation test give us even more accurate results and the procedure is used for biochemical family screening.6,7 MTC occurs as a sporadic tumor or in hereditary settings MEN 2A, MEN 2B and FMCT.3,4,8,9 Germ-line point mutations in RET proto-oncogene are responsible for tumor arise and inheritance of settings. Genetic screening provides information of these RET mutations in family members even before pathologic changes occur. These individuals with MEN 2A, 2B and FMCT characteristic RET mutations are almost certain to acquire MTC (95% penetrance) in their lives and are candidates for preventive total thyroidectomy (TT), with or without central neck dissection (CND).10,11 Surgery as the treatment of choice for MTC and only C-cell hyperplasia and early stage of MTC can be cured. Prophylactic thyroid surgery eliminates the possibility of MTC but doesn't influence appearance of other diseases (PHEO, HPTH) of MEN 2 syndromes.2,12-18

Key words: medullary thyroid carcinoma, genetic

MATERIAL AND METHODS

During the period 1969-2002, 105 patients with MTC from 88 families, were treated and/or diagnosed at the Institute of Oncology Ljubljana, Slovenia. Medical records of patients with inherited forms of MTC confirmed by genetic tests were studied, and cases of prophylactic thyroid surgery were pointed out.

Each our patient with MTC was regarded as an index member of an affected family until it was proven to the contrary. Informal consent for genetic testing was obtained from 58/88 index patients - from all who were alive and reachable during the period 1997-2002.

From 1997 onwards genetic testing was performed in 58/88 MTC index patients. In the group of tested patients there were 24 males (16-93y) and 34 females (23-77y) from 58 families and their 50 kindred, aged 8-67y. Twenty-five/50 kindred were members of MTC families where germline mutations of RET proto-oncogene were found.

Three affected families were detected by biochemical screening before the genetic one was introduced at our institution, late in 1996. MTC was diagnosed in 8 patients (3 pts MEN 2A, 4 pts FMCT and 1 patient MEN 2B). Patient with MEN 2B syndrome and two with MEN 2A died and were not included in genetic testing while in 5/8 patients clinical settings were later confirmed by genetic tests. The genetic tests were performed at the Institute of Pathology, Medical Faculty as described previously.16,20 When specific RET proto-oncogene mutations were found, genetic testing was repeated (including new blood sample) in order to exclude the possibility of technical faults. Pheochromocytoma (PHEO) was excluded and essential diagnostic work up (TC blood levels determination, US of the neck and FNAB of visualized tumor) for MTC was carried out. When MTC was diagnosed and/or in case of positive genetic result, thyroid surgery was indicated. TT with CND was the minimal surgical procedure. Thyroidectomy was considered prophylactic when surgery was indicated only in view of genetic test results with no evidence of MTC on permanent histology.

RESULTS

Germline mutations of RET proto-oncogene were found in 12/58 (20, 6%) MTC index patients - 2 males (16 and 65y) and 10 females (23-55y, median 36y). Among these patients, two index patients primary classified as sporadic MTC were also found to have germline mutations. All patients had thyroid tumor and 4/12 had also lymph node metastases. In 12 affected families informal consent was
obtained from 8 families and genetic screening was performed in 25 kindred of 7 families.

This group included 13 males aged 8-57 years (median 21.5) and 12 females aged 8-54 years (median 20.5). The germline RET gene mutations were found in 14/25 kindred - 5 males aged 18-57 years (median 21) and 9 females aged 12-54 years (median 41) but were absent in 11/25 kindred.

Serum TC values, stimulated and/or basal were pathologic in 11/14 kindred and imaging diagnostic showed tumors in 10/14. One 14 individual had enlarged neck lymph nodes.

MEN 2A was expressed in 3/14 kindred (3 PHEO and 1/3 HPTH) with codon 634 mutations only.

Genetic screening results indicate thyroid surgery in all 14 kindred; in 11/14 patients MTC was suspected or diagnosed.

After diagnostic work-up only 3/14 affected kindred were candidate for prophylactic thyroid surgery. There were female kindred aged 12, 20 and 51 years with codon 618 and twice 790 mutations respectively. First two were second generation and their mothers were index cases. The third candidate for prophylactic thyroid surgery was mother of the index patient aged 16. She had multinodular goiter but no clinical or biochemical evidence for CCH or MTC.

TT with CND was performed in all three affected kindred without any surgical complications. Permanent histology showed no evidence of CCH and MTC even after immunohistochemical staining for calcitonin.

**DISCUSSION**

MTC is potentially killing tumor. Its biological behavior is generally somewhere between anaplastic and well-differentiated thyroid carcinoma and shows great clinical variability. MTC occurs either as a sporadic or hereditary entity, which represents approximately 25% of all.2,4,10,18,21,25 Stage of disease at presentation is one of the most important prognostic factors.2,3,4,23,24

Overall 5-years survival rates of 67%-86% were reported in some retrospective studies with better results when patients with early MTC, found by screening, were included. Only familial forms of MTC can be detected in earlier stage by screening.22,25 Biochemical screening of MTC family detects members with C-cell hyperplasia and/or minimal carcinomas while genetic screening can detect kindred with specific RET proto-oncogene mutations even before pathologic changes occur in their thyroids.2,5,26,27

Genetic testing should not have false negative or positive results when performed properly using RET analyses, taking also sample mix-up and false paternity into consideration.2,24,5,8,10,14,15,26,28

Only 25 kindred of our 12 index patients take a part in genetic screening. Low kindred compliance and small families in Slovenia can be explanations for such number. RET gene mutations were detected in 14/25. Unfortunately, MTC was clinically and/or biochemically suspected preoperatively in 11/14 gene carriers. Later the diagnose MTC was confirmed by histology and intended prophylactic thyroid surgery, turned to be curative one in these cases.

Three/14 from our affected kindred fulfilled the conditions for prophylactic thyroid surgery. Codon 618 mutation was found in 12 old girl and codon 790 mutations in 20 an 51 years old ladies. All were FMTC families' members. TT and CND were performed in all three cases and there were no evidence of MTC; even no evidence of C-cell hyperplasia. These are rare conditions and technical mistakes were ruled out by repeated genetic tests. It would be possible to explain normal thyroid histology in the case of 12 years girl as a preclinical phase of C-cell hyperplasia/MTC, but almost impossible for 51 years old lady with codon 790 mutation and nodular goiter which was after surgery examined in details including immunohistochemical analysis. Her son was an index patient at the age of 16, presented with stage 2 MTC, gigantc figure and knee problems. Different expression of mutated RET gene can be the explanation for normal thyroid histology (regarding C-cell pathology) in his mother's case. Some other reports support this theory. Probably the same explanation can valid for our 20 years old lady with codon 790 mutations, whose 41 years old mother was the MTC index patient.30,11

Our youngest gene carrier was 12 and so far we do not have our own experience in prophylactic thyroid surgery in children less then 10 years old. We agree that genetic testing should be performed as soon as possible but timing for prophylactic surgery should consider patient's RET gene mutation.30,12 There is no doubt that MEN 2B needs aggressive surgery as soon as genetic results are available. In these cases surgery should be prophylactic only in the first year of life by most reports and for MEN 2A at age 5-6 years.2,13,21,32,36 Familial forms of MTC seemed more heterogeneous in appearance and clinical course, also by our experiences. FMTC resulted codon 790 and 791 mutations were pointed out as an examples.2,12

**SUMMARY**

Medullary thyroid carcinoma (MTC) occurs sporadically or is inherited as a characteristic component of MEN 2A, MEN 2B and familial MTC. Germline point mutations in RET proto-oncogene are responsible for tumor arise and inheritance. Genetic screening provides information of these RET mutations in family members even before pathologic changes of C-cells progress to MTC.

The aim of our study was to identify carriers of RET gene mutations in our patients with MTC and their kindred. Surgical therapy was based on genetic testing results and clinical features. Prophylactic thyroid surgery was the subject of interest.

From 1969-2002 105 patients with MTC (88 families), were treated and/or diagnosed at the institute of Oncology Ljubljana, Slovenia. Genetic testing was so performed in 58/88 MTC index patients (24 males (16-93y) and 34 females (23-77y)) and their 50 kindred, aged 8-67y. Twentysfive/50 kindred were from affected families.
Germline mutations of RET proto-onkogene were found in 12:58 (20.6%) MTC index patients - 2 males (16 and 65 y) and 10 females (23-55y, median 36y) and in 14:25 kindred from 12 affected families - 5 males aged 18-57 years (median 21) and 9 females aged 12-54 years (median 41) but were absent in 11:25 kindred.

Genetic screening results indicate thyroid surgery in all 14 kindred; also MTC was clinically suspected or diagnosed in 11:14 patients and 3:14 were candidates for prophylactic thyroidectomy. Total thyroidectomy with central neck dissection was the minimal surgical procedure.

Prophylactic thyroidectomy based on genetic testing results allows earlier diagnosis and treatment of patients, even before pathologic changes of C-cells occur. Patient’s age and codon mutation influence the timing of surgery and even it’s extend.

REZIME

Medullarni tiroidni karcinom (MTC) se javlja sporadično ili se nasleduje kao karakteristična komponenta MEN 2A, MEN 2B in hereditarnem MTC. Germ/line point mutacije kod RET proto-onkogene su odgovorne za pojavu tumor a in njegovo nasledovanje. Genetski skrining obezbeđuje informacije o ovim RET mutacijama u okviru članova porodice in pre na to bi patološke promene C-celija dovede do MTC-a.

Cilj ovog rada je da identifikuje nosioce RET genetskih mutacija kod bolesnika obeholih od MTC in njihovih potomak. Hirurško lečenje je bilo bazirano na rezultatih genetskega testiranja in kliničkih znakova. Profilaktična tiroidna hirurška je bio predmet interesovanja.

U periodu od 1969 do 2002., 105 bolesnika sa MTC-om (88 familija) je dijagnostikovano in/ili hirurško lečeno na Institutu za Onkologiju Ljubljana, Slovenija. Genetsko testiranje je sprovedeno kod 58:88 MTC bolesnika (24 muškog pola (16-93 godine starosti)) in 34 ženskega pola (23-77 godina starosti) in 50 njihovih potomak starosti od 8 godina do 67 godina. 25:50 je bilo iz familij obeholih od MTC.


Rezultati genetskog skrininga indikovali su tiroidnu hiruršku kod svih 14 potomaka. Takojče, na MTC je sumnjano ili je klinički dijagnostikovano kod 11/14 bolesnika, a 3/14 su bili kandidati za profilaktičku tiroidektomi.

Totalna tireoidektomija sa centralnom rezekcijom vrata je bila najmanje zastupljena hirurška metoda. Profilaktička tireoidektomija bazirana na genetskom skriningu dozvoljava ranu dijagnozou i tretman bolesnika, čak in pre nego nastanec patološke promene C-celija. Starost bolesnika in kodon mutacije diktiraju vreme hirurškog zahvata in obim.

BIBLIOGRAPHY


