FAMILIAL NONMEDULLARY THYROID CANCER

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FAMILIAL NONMEDULLARY THYROID CANCER (Abstract): Follicular cell-derived thyroid cancer which represents 90-95% of all thyroid malignancies may occur in at least 5% of cases as familial disease. Familial nonmedullary thyroid cancer (FNMTCH) is defined as the existence of two or more first degree relatives affected within a family. FNMTCH may occur in two situations: pure FNMTCH in which FNMTCH is the predominant neoplasm although other cancers may occur with increased frequency (non syndromic NMTC) and syndromic NMTC in which other cancers or association of tumors are the most predominant feature and thyroid cancer is associated with known frequency. Most patients with syndromic NMTCs are asymptomatic, but genetic screening for the syndrome allows an early diagnosis and adequate surgery. Syndromic and non-syndromic FNMTCH may represent 5-15% from all follicular cell-derived thyroid carcinomas. Four susceptibility loci for pure FNMTCH have been described: TCO – familial thyroid carcinoma with oxyphilia on chromosome 19p13.2, FPTC/PRN – familial papillary thyroid carcinoma with papillary renal neoplasia (carcinoma) on chromosome 1q13.2-1q22, NMTC1 – non medullary thyroid carcinoma type 1 on chromosome 2q21, NMG1 – multinodular goiter with papillary thyroid carcinoma on chromosome 14q32. Inheritance is autosomal dominant, but the candidate genes are unknown. Most authors agree that pure FNMTCH have a more aggressive behavior: multifocality, bilaterality, association with other thyroid disease (nodules and thyroiditis), trend to spread locally and in lymph nodes, higher recurrence rate, lower disease-free survival. Syndromic FNMTCHs occur in the following syndromes in which FNMTCH occurs with a known frequency: Familial Adenomatous Polyposis and Gardner’s syndrome (associated FNMTCH - 5%), PTEN-hamartoma tumor syndrome (PTEN/PHTS - associated FNMTCH - 10%), Carney’s complex (associated FNMTCH - 10-25%), Werner’s syndrome (associated FNMTCH - up to 18%). Knowing the aggressiveness of FNMTCHs, affected individuals must be prospectively researched by screening, aggressively treated and closely monitored. Their relatives must be also monitored for early diagnosis known the phenomenon of genetic anticipation.

KEY WORDS: FAMILIAL NONMEDULLARY THYROID CANCER; FNMTCH; FAMILIAL ADENOMATOUS POLYPOSIS; PTEN-HAMARTOMA TUMOR SYNDROME; CARNEY’S COMPLEX; WERNER’S SYNDROME.

SHORT TITLE: Familial nonmedullary thyroid cancer


INTRODUCTION

Follicular cell-derived thyroid cancer represents 90-95% of all thyroid malignancies and at least 5% are familial diseases [1-3]. Among thyroid cancer papillary form the most frequent type. After introduction of thyroid ultrasound in the routine examination thyroid cancer became the cancer with the highest increase in prevalence in the last years [1]. Although most of thyroid cancers occur as sporadic forms, familial nonmedullary thyroid cancers (FNMTCH) have been described by Stoffer (1986), Loh (1997) quoted by Capezzone (2008), and seem to be more common than previously thought [4]. The first definition of follicular cell-derived thyroid carcinoma was that of occurrence of in more than one member of a
family but was criticized because the presence of only 2 affected individual could be a simply fortuitous association.

Now FNMTC is defined as the existence of two or more first degree relatives affected within a family [cited by 4] or as follicular cell-derived cancers in three or more first degree relatives in a family [5,6]. After Capezzone (2009) only seven families with three or more affected members may be considered for clinical and genetic screening for non-syndromic FNMTC [7]. FNMTC may occur in two situations: pure FNMTC in which FNMTC is the predominant neoplasm although other cancers may occur with increased frequency (non syndromic NMTC) and syndromic NMTC in which other cancers or association of tumors are the most predominant feature and thyroid cancer is associated with known frequency [2,5,7,8]. Most patients with syndromic NMTCs are asymptomatic, but genetic screening for the syndrome allows an early diagnosis and adequate surgery [5].

Classification of FNMTC (after Nose and Capezzone) [3,5,7]:

A) Non-syndromic: familial tumor syndromes with preponderance of NMTC
   1) Familial papillary thyroid carcinoma with or without oxyphilia- FPTC
   2) FPTC associated with renal papillary neoplasia
   3) Familial NMTC type 1
   4) FPTC with multinodular goiter

B) Syndromic: familial tumor syndromes with preponderance of non-thyroidal tumors and in which NMTC occurs with a known frequency:
   1) Familial adenomatous polyposis (FAP) and Gardner’s syndrome (a FAP variant)
   2) PTEN-hamartoma tumor syndrome (Cowden’s syndrome)
   3) Carney’s complex
   4) Werner’s syndrome
   5) Pendred syndrome

FREQUENCY OF NMTC
The risk of developing NMTC among first degree relatives of an affected individual is 3-9 folds higher than in individuals with no affected relative and the frequency of familial papillary thyroid cancer is the highest of all cancer types [4]. The frequency of FNMTC is reported in the literature as follows:

Syndromic and non-syndromic FNMTC may represent 5-15% of all follicular cell-derived thyroid carcinomas. Non-syndromic FNMTC represents 10.5% of these carcinomas [5]. Five percents of thyroid cancers have an evidence of familial association [1,2,9,10] and 5% of NMTC could be diagnosed on the basis of familial predisposition [11]. FNMTCs represent 8.8% of all thyroid cancers and 9.4% of patients with only papillary thyroid cancers [12].

GENETICS OF FNMTC

Pure (non-syndromic) FNMTC
Population-based studies suggest that pure FNMTC is a true hereditary syndrome [13] which has an autosomal dominant inheritance with reduced penetrance or age-related partial penetrance [14]. Four susceptibility loci for non-syndromic NMTC have been described in different families but real genetic defects are still not demonstrated [1,3-5,10,15,16]:

TCO – familial thyroid carcinoma with oxyphilia on chromosome 19p13.2. Inheritance is autosomal dominant but candidate gene is not known.

FPTC/PRN – familial papillary thyroid carcinoma with papillary renal neoplasia (carcinoma) on chromosome 1q13.2-1q22. Type of inheritance is autosomal dominant, candidate gene is unknown. Papillary renal neoplasia has a close histology with that of papillary thyroid carcinoma [9]. Other neoplasm may be associated with FPTC/PRN [5].

NMTC1 – non medullary thyroid carcinoma type 1 on chromosome 2q11. Inheritance and candidate gene is not known.

NMG1 – multinodular goiter with papillary thyroid carcinoma on chromosome 14q32. Inheritance is autosomal dominant, but the candidate gene is unknown.
Microsatellite linkage analysis allowed the description of other candidate loci and genes for FNMT such as: FTEN on chromosome 8p23.1, genes on chromosomes 1q.21 and 6q.22 [10]. FPTC was associated with germ-line imbalanced telomere-telomerase complex with increased copy number and expression of telomerase when compared with sporadic PTC [4].

The analysis of different familial cases of FNMTCs by linkage desechilibrium and loss of heterozigosity showed that above-mentioned mutations are not as frequent as previously thought, but BRAF V600 and RAS mutations already known to be involved in sporadic PTC tumorigenesis have been found1.

In a study on 14 individuals with FNMTC 35% had loss of heterozigosity for three susceptibility loci: NMTC1, TCO and MNG1 and 41.4% had BRAF V600 mutations [11]. In other study, Xing on 40 cases of FNMTC, no BRAF mutation was found [cited by 16]. In syndromic FNMTCs there have been not found mutations for the following genes [1,15]: RET, MET, MEK1, MEK2, TRKA/NTR1C, TSH-R, PTEN or APC.

TUMOR CHARACTERISTICS IN FNMTC

FNMTCs show a general characteristic of “genetic anticipation” defined by Mc Innis 1996 [cited by 4] as “occurrence of a genetic disorder at progressively earlier age and increased aggressiveness in successive generations”. Cohort-based studies on FNMTCs have shown some characteristics which involve a specific approach of these tumors [4,5,13,17]:

- tumors are more frequently multifocal and bilateral;
- in the offsprings they appear at younger ages and have a more aggressive behavior (especially if a proband was already seen in the family) [4,18]; the aggressiveness of FNMTCs compared with sporadic disease is controversial, but may be more important if the index case in families with 3 or more affected individuals [13] or in another study the aggressiveness of FNMTC is independent of affected members in the family [19].
- FNMTCs have more frequent ipsilateral and controlateral lymph node involvement and local invasion that explain a higher recurrence rate, a worse outcome and a shorter disease-free survival [4,5,10,17,19].
- association with other thyroid disorders. Thyroid autoimmunity is higher in families with more than one affected member [20]. Compared with sporadic disease FNMTC occurs more frequently in association with multiple benign adenomatous nodules, multinodular hyperplasia and lymphocytic thyroiditis [17,21]. An analysis of 50 individuals with FNMTCs in 8 families showed that 26% of them have more than one thyroid lesion [8].

A study including 1502 individuals with follicular cell-derived thyroid cancers Mazeh demonstrated in those with FNMTC compared with sporadic forms the following characteristics [19]: multicentricity - 48% vs 22%, local invasion - 54% vs 0.6%, more frequent local invasion and higher recurrence rate - 24% vs 12%. Zhao J. in study of 36 FPTCs from 15 families has found: bilaterality in 33.3% of cases, multifocality in 55.6%, lymph node metastases in 75%, coexistence with benign thyroid lesions in 27% of cases [21].

The main features of FNMTCs were summarized by Nose and Mc Donald as follows [5,6]:

- early age of diagnosis;
- association with benign thyroid diseases;
- higher male to female ration than usually seen in thyroid cancer;
- multifocality and bilaterality;
- more aggressive behavior;
- higher trend to spread out of the thyroid;
- higher rate of distant metastases;
- higher rate of persistence and recurrence;
- lower survival rate;
- only candidate locuses without candidate genes.

Taking into account these features, FNMTCs must be aggressively treated by total thyroidectomy, central compartment neck dissection, lateral functional (modified) neck dissection [15], radioiodine postoperative ablation, TSH suppressive treatment and close thyroglobulin monitoring [8,18]. Clinical and neck ultrasound monitoring of the relatives are mandatory [18].

SYNDROMIC NMTC

1. Familial adenomatous polyposis (FAP) and Gardner’s syndrome (a FAP variant) are autosomal dominant syndromes due to APC (Adenomatous Polyposis Coli) tumor suppressor gene located on the chromosome 5q21. Birth incidence of the disease varies from 1/8300 to 1/11300-1/37000 [22]. Classic FAP becomes manifested from the second decade of life by the appearance of thousands of adenomatous polyps in the colon and rectum. Attenuated FAP (AFAP) shows fewer adenomatous polyps, later age of appearance and lower cancer risk [22]. Gardner’s syndrome is a variant of FAP that includes other diseases. 5% of patients with FAP develop follicular cell-derived thyroid carcinomas. 1-2% develops PTC [23]. Extrathyroidal diseases may be: osteomas of the mandible, fibrous dysplasia of the skull, fibrous dermoid tumors, hypertrophic retinal pigmented epiphyelium [5]. FAP associated PTC shows a particular histology: the cribriform-morular varian or may be a classic PTC with sclerosis [24].

2. PTEN-hamartoma tumor syndrome (PTEN/PHTS) is an autosomal dominant inherited syndrome due to gene deletion of PTEN (Phosphatase and Tensin homolog) tumor suppressor gene located on chromosome 10p23.2. It includes Cowden’s syndrome (CS), Bannayan – Riley – Ruvalcalba syndrome, Proteus syndrome and Proteus-like syndrome [5,25].

PTEN is a phosphatase for phosphoinositol 3,4,5 triphosphate involved in cell cycle, genomic stability and apoptosis [26]. Non thyroidal diseases in the PTEN-hamartoma tumor syndrome are [5,25,27]: hamartoma of the breast, colon, endometrium, uterus, brain, hemangiomias, lipomatisis. 10% of those with Cowden syndrome may develop follicular cell-derived thyroid carcinoma [5]. Thyroid in Cowden’s syndrome may have multiple adenomatous nodules, follicular nodules, lymphocytic thyroditis. The thyroid cancer may be papillary (60%) or follicular (40%). After Harb [23] up to 10% of patients with Cowden’s syndrome may have follicular carcinoma. Loss of function PTEN mutation may be identified by immunohistochemistry with a sensitivity of 100% and a specificity of 92.3% [27]. Thyroid carcinoma has the highest familial incidence in CS. Out of 2723 patients with CS 664 had thyroid cancer. PTEN mutation is associated with a nine fold increase of risk for pediatric thyroid cancer. Close surveillance of children carrying PTEN/PHTS mutation must begin as soon as mutation is detected [28], at the age of 18 years or 5 years before the age of the earliest detect case in the family [26]. Individuals with PTEN germ-line mutation must be monitored followed for cancer following specific recommendations [29].

3. Carney’s complex is an autosomal dominantly inherited syndrome due to PCKR1-x (proteininikinase A regulatory subunit type 1α) situated on chromosome 2p16 [5,30]. 500 cases have been registered in the NIH-Mayo Clinic and Cochrane database. Non thyroidal illnesses in the syndrome may be [5,30]: primary pigmented adrenocortical disease (60-75%), cardiac mixoma, skin mixoma, lentigiosis, blue nevi, pituitary adenomas (acromegaly), testicular tumors, ovarian cysts. The incidence of thyroid cancer in the syndrome varies between 4 and 60% [5] or 10-25 % [30] and the carcinoma may be of papillary
or follicular type [5]. Papillary thyroid cancers have an aggressive behavior in Carney’s complex [30].

4. Werner’s syndrome (WS) is produced by mutation of WRN gene situated on chromosome 8p11-p12. The main features of WS are [5,31]: abnormal body habitus (short stature, stocky trunk and spindly limbs), premature aging (grey hair, cataracts, osteoporosis) sleroderma-like changes of the skin, muscular atrophy and endocrine diseases: diabetes mellitus, hypogonadism [5,31]. The incidence of thyroid cancer in WS is up to 18% (3% in non Japanese and 14% in Japanese population) and the histology may be: PTC: 84%, follicular: 14 %, anaplastic 20% [5].

5. Pendred’s syndrome (PS) is an autosomal recessive disease caused by mutation of LSC26A4 gene which encodes pendrin, a gene involved in iodide organification in the thyroid and in the maintenance of normal anion transport and endocochlear potential in the inner ear [32,33]. PS is characterized by bilateral sensoneuronal deafness, goiter and hypothyroidism. Follicular thyroid carcinoma and Hurthle cell carcinoma were described in 6 Thai families with PS by Snabboon T [34] and in an isolated case of PS by Bashir [35].

CONCLUSIONS
Follicular cell-derived thyroid cancer has the highest increase in prevalence during last years due to routine ultrasound examination of the thyroid gland. 5-10 % of nonmedullary thyroid carcinomas may be familial forms, defined as three or more affected individuals in a family. Relatives of patients with FNMTCs have a 3-9 fold increased risk of developing the same disease, which seems to be the highest risk among all cancers.

Familial thyroid cancer occurs as non-syndromic (pure) form in which thyroid cancer is the predominant feature or as syndromic forms in which other malignancies are predominant and thyroid cancer is associated with a known frequency.

Although at least four susceptibility loci are probably involved in the occurrence of pure, non-syndromic thyroid cancer (TCO, FPTC/PRN, NMTC1, MNG1) the candidate gene have not been described until now. The inheritance seems to be autosomal dominant with reduced penetrance or age-related penetrance.

The main features of pure familial thyroid cancers are: the association with other thyroid disease: nodular and autoimmune diseases, bilaterality, multicentricity, more aggressive behavior with trend to spread out of the thyroid, greater rate of persistence and recurrence within thyroid bed, frequent distant metastases and lower survival rate.

Knowing the aggressiveness of FNMTCs, affected individuals must be prospectively researched by screening, aggressively treated and closely monitored. Their relatives must be also monitored for early diagnosis known the phenomenon of genetic anticipation.

CONFLICT OF INTERESTS
None to declare

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