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Prophylactic Thyroidectomy for Asymptomatic 3-Year-Old Boy with Positive Multiple Endocrine Neoplasia Type 2A Mutation (Codon 634)

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SUMMARY

Introduction The multiple endocrine neoplasia type 2A (MEN 2A) syndrome, comprising medullary thyroid carcinoma (MTC), pheochromocytoma and primary hyperparathyroidism (PHPT) is most frequently caused by codon 634 activating mutations of the RET (rearranged during transfection) proto-oncogene on chromosome 10. For this codon-mutation carriers, earlier thyroidectomy (before the age of 5 years) would be advantageous in limiting the potential for the development of MTC as well as parathyroid adenomas.

Case Outline This is a case report of 3-year-old boy from the MEN 2A family (the boy's father and grandmother and paternal aunt) in which cysteine substitutes for phenylalanine at codon 634 in exon 11 of the RET proto-oncogene, who underwent thyroidectomy solely on the basis of genetic information. A boy had no thyromegaly, thyroidal irregularities or lymphadenopathy and no abnormality on the neck ultrasound examination. The pathology finding of thyroid gland was negative for MTC. Two years after total thyroidectomy, 5-year-old boy is healthy with permanent thyroxine replacement. His serum calcitonin level is <2 pg/ml (normal <13 pg/ml), has normal serum calcium and parathyroid hormone levels and negative urinary catecholamines. Long-term follow-up of this patient is required to determine whether very early thyroidectomy improves the long-term outcome of PHPT.

Conclusion Children with familial antecedents of MEN 2A should be genetically studied for the purpose of determining the risk of MTC and assessing the possibilities of making prophylactic thyroidectomy before the age of 5 years.

Keywords: MEN 2A; prophylactic thyroidectomy; medullary thyroid carcinoma; genetic screening; child

INTRODUCTION

The multiple endocrine neoplasia type 2A syndrome (MEN 2A), comprising medullary thyroid carcinoma (MTC), pheochromocytoma (PHE) and primary hyperparathyroidism (PHPT), is inherited in autosomal dominant fashion on chromosome 10 [1, 2]. The specific genetic abnormality was initially localized to a site close to the centromere of chromosome 10 [1, 2]. More recently, it has been identified as a mutation (most commonly exons 10 and 11) in the rearranged during transfection (RET) proto-oncogene [3]. In MEN 2A, the most frequent germ line mutations involve the extracellular domain of RET at codons 634, 620 and 618 [3]. As the invariable component of MEN 2, MTC is present in all affected individuals whereas adrenal PHEs and PHPT occur in only 50% and 10% to 30%, respectively [4].

Previously, the presence of MTC within a family member could only be confirmed by detection of clinical disease (goiter or cervical lymphadenopathy) or by the elevated levels of plasma calcitonin measured basally or following stimulation with a calcitonin secretagogue such as pentagastrin or calcium. Identification of the specific genetic defect in MEN 2A now permits diagnosis of the syndrome, following routine blood sampling, in patients who may have no clinical or biochemical stigmata of disease. We record the management of a 3-year-old boy from a MEN 2A family (codon 634), who underwent thyroidectomy solely on the basis of genetic information. Prophylactic thyroidectomy before the age of 5 has been recommended by the American Thyroid Association (ATA) [5].

CASE REPORT

Screening of 3-year-old boy of the MEN 2A family member revealed the presence of 634 Cys-Phe mutation within the RET gene. His elder 6-year-old sister was found not to be affected. The family history of affected paternal relatives included a father with MTC and PHE, grand-mother with MTC and paternal aunt with MTC and PHE. A boy had no thyromegaly, thyroidal irregularities or lymphadenopathy and no abnormality on

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the neck ultrasound examination. His initial basal serum calcitonin was mildly elevated -19.5 pg/ml (normal <13 pg/ml). Total calcium (TCa) and parathyroid hormone (PTH) values were normal (TCa 2.2 mmol/l, normal 2.02-2.6 mmol/l; PTH 25 ng/l, normal 15-65 ng/l). Pentagastrin stimulation testing, which often results in significant retrosternal and abdominal discomfort, had not been carried out in this child. Urinary catecholamines levels were normal. Following appropriate discussion with parents, and solely on the basis of genetic information and recommendation of ATA consensus group, total thyroidectomy was carried out. The surgical pathology was insignificant for 2.17-g thyroid gland with normal histopathologic findings. The patient developed postoperative hypocalcemia for which both oral calcium and vitamin D supplementation was given. After one month of therapy, with tapering of the oral calcium and vitamin D doses, the treatment was discontinued. Two years after total thyroidectomy, this 5-year-old boy is healthy with permanent thyroxine replacement. His calcitonin level is <2 pg/ml, has normal calcium and PTH hormone levels and negative urinary catecholamines.

DISCUSSION

In MEN 2 mutation carriers, the timing of thyroidectomy depends on the type of RET mutation and the earliest observed occurrence of MTC in patients with the mutation. RET mutations have been shown to be closely associated with specific phenotypes, age of disease onset, and aggressiveness of the disease [4]. It is recommended that routine RET mutation analysis should be performed in all apparently sporadic cases of MTC where the prevalence of familial disease is reported to be between 6% and 25% [5].

The American Thyroid Association has recently updated the classification system to incorporate all known mutations in MEN 2A and recognize more aggressive natural history of codon 634 mutations [5]. A Task Force Committee also introduced an updated set of recommendations for the timing of prophylactic thyroidectomy based on the specific mutation as well as on certain clinical risk factors including patient's age, family history, radiographic findings and serum calcitonin level: risk level A (codons 768, 790, 791, 804 and 891), risk level B (codons 609, 611, 618, 620 and 630) and the highest risk level C (codon 634). The recommendations considered not to allow delay in thyroidectomy for the risk level C. Patients with 634 codon mutations have earlier progression from C-cell hyperplasia to MTC and higher rates of metastatic disease when compared with patients with other mutates codons from the extracellular domain of chromosome 10 [6]. For this codon-mutation carriers, earlier thyroidectomy (before 5 years of age) would be advantageous in limiting the potential for development of metastatic MTC as well as parathyroid adenomas [7, 8]. At risk levels A and B, C cell disease may appear later in life and thyroidectomy may be performed later in life, depending on calcitonin levels, neck ultrasound findings, family history and family preference.

However, some barriers to earlier thyroidectomy are the morbidity associated with pediatric anesthesia, especially in young infants, as well as surgical risks of recurrent laryngeal nerve palsy and hypocalcemia. The risk of these complications, when thyroidectomy is performed under the care of pediatric-trained anesthetists and surgeons, does not outweigh the benefits of prophylactic thyroidectomy in the affected carriers of 634 codon mutation [6, 7, 8].

In children from MEN 2A kindred, MTC has been found to occur as early as 1 year of age, although nodal invasion rarely develops before adolescence. Once malignant transformation is present, the rate of progression to nodal metastases is estimated to be 6.6 years later [9]. Indeed, lymph node metastases are uncommon in patients with thyroid tumor foci less than 5 mm in diameter and basal calcitonin levels below 40 pg/ml [3]. PHEs and PHPT occur later in childhood; PHE has been identified in a child as early as 12 years old and PHPT in a 10-year-old child [3, 9].

In the present paper, a 3-year-old boy of the MEN 2A family in which cysteine (TGC) substitutes for phenylalanine (TTC) at codon 634 in exon 11 of the RET proto-oncogene, has undergone prophylactic thyroidectomy. The boy manifested no abnormalities on physical examination. He had mildly elevated preoperative calcitonin, aggressive family history and 634 codon mutations (risk level C). The pathology finding was negative for MTC despite elevated preoperative calcitonin. It should be stressed that elevated calcitonin or more histological data for a thyroid specimen may indicate C cell hyperplasia. Furthermore, if the suggestion by Iler et al was correct, prevention of MTC might be also preventive of PHPT [9], although surveillance of this boy would include measurement of PTH hormone levels. Prophylactic thyroidectomy in our patient was exclusively on the basis of the genetic information, supporting the belief that thyroidectomy could be appropriate at an even younger age under circumstances. Long-term follow-up of this patient is required to determine whether very early thyroidectomy improves the long-term outcome of PHPT.

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Профилактичка тиреоидектомија код асимптоматског трогодишњег дечака с позитивном мутацијом за мултиплу ендокрину неоплазију 2А (кодон 634)

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КРАТАК САДРЖАЈ

Увод Синдром мултипле ендокрине неоплазије тип 2А (МЕН 2А), који обухвата медуларни тиреоидни карцином (МТК), феохромоцитом и примарни хиперпаратиреоидизам (ПХП), најчешће је узрокован активном мутацијом на кодону 634 *RET* (реаранжиран током трансфекције) протоонкогену хромозома 10. Код носилаца ове мутације профилактичка тиреоидектомија у ранијем узрасту (млађем од пет година) смањује потенцијал за развој МТК, као и паратиреоидног аденома.

Приказ болесника Приказали смо трогодишњег дечака из породице са МЕН 2А (дечаков отац и баба и очева тетка) код којег је цистеин замењен фенилаланином на кодону 634, егзон 11, на *RET* протоонкогену, код којег је урађена профилактичка тиреоидектомија искључиво на основу генетских података. Дечак није имао тиреомегалију, био је нормалног тиреоидног статуса без лимфаденопатије и нормалног ултразвучног налаза врата. Хистопатолошки налаз је био негативан за МТК. Две године након тоталне тиреоидектомије петогодишњи дечак је здрав и свакодневно прима супституциону терапију тироксином. Његов ниво калцитонина је мањи од 2 *pg/ml* (нормална вредност <13 *pg/ml*), ниво калцијума и паратиреоидног хормона је нормалан, а катехоламини у мокраћи негативни. Дугорочним клиничким праћењем овог болесника ће се утврдити да ли је рана профилактичка тиреоидектомија побољшала дугорочно исход за ПХП.

Закључак Код деце са породичним МЕН 2А треба урадити генетску дијагностику ради утврђивања ризика за развој МТК и ради процене могућности примене профилактичке тиреоидектомије пре пете године живота.

Кључне речи: МЕН 2А; профилактичка тиреоидектомија; медуларни карцином штитасте жлезде; генетски скрининг; деца

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