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Familial Thyroid Cancer in Children (About 3 Cases)

Sarah Hosni*, Driss Hanine, Rachid Oulahyane, Mounir Kisra
Visceral Pediatric Surgery Service « A » - Children Hospital of Rabat Morocco

Original Research Article

***Corresponding author**
Sarah Hosni

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Abstract: Genetic predispositions are present in 10% of children with cancer worldwide. In our study, we were interested in familial thyroid cancers and more specifically in medullary thyroid cancer. Medullary thyroid cancer, despite its rarity, arouses great interest, given its inheritance in more than 25% of cases. This cancer is often caused by multiple endocrine neoplasia type 2, related to a mutation of proto-oncogene RET. This work is based on two parts: a literature review and our retrospective study of three children hospitalized in the child surgery department at the Rabat Children's Hospital. Subjects underwent total thyroidectomy for curative treatment of medullary thyroid cancer for one case and prophylactic for two carriers of multiple endocrine neoplasia type 2A The bibliographic results are consistent with the epidemiological, clinical and paraclinical, genetic and therapeutic results of our study. The genetic study of these familial cancers makes it possible to better target the indications for surgical management. In the face of these genetic predispositions, some studies recommend that children be cared for, as well as their families, who have a risk factor in the broad sense. Thanks to the emergence of new techniques such as the sequencing of the new generation, it is likely that new susceptibility genes will be discovered and will explain new family cases, with the possibility of genetic counseling. Oncogenetic department should be in our hospital, allowing prevention and early diagnosis of familial cancers, as well as the study of genetic variations for more targeted therapeutic management.
Keywords: thyroid carcinoma, familial, prophylactic surgery, oncogenetic.

INTRODUCTION

The percentage of childhood cancers due to genetic predisposition or familial cancers varies from study to study. Family cancers have guidance criteria for proper management of the subject and family members, so we have retained age (earlier than usual), bifocality or bilaterality, association with another cancer of other organs as well as a family history of cancers.

It should be noted that among the various types of thyroid cancer, spinal cord cancer is almost always hereditary in children, and is a multiple endocrine neoplasia type 2A and 2B, related to a germ line mutation dominance of a RET proto-oncogene, hence the interest of our study.

Medullary thyroid cancer accounts for 5 to 10% of thyroid cancers, which have a 4.9% incidence of all cancers in children and adolescents. Despite the low incidence of spinal cord cancer compared to differentiated thyroid cancers, familial forms of CMT predominate in familial forms of the latter.

The objectives of this study are primarily to describe the epidemiological, clinical, para-clinical and genetic aspects of familial medullary carcinoma of the thyroid, and secondly their prophylactic and curative management. Finally, the contribution of genetics in the personalization of the surgical management of familial thyroid cancers.

MATERIELS & METHODS

Our study runs from January 2008 to July 2016 in the pediatric visceral surgery department "A" at the Children's Hospital of Rabat, the cases studied are 2 subjects, brother and sister, presenting a neoplasia endocrine type 2A with C-cell hyperplasia requiring prophylactic thyroidectomy and a case with familial probably thyroid carcinoma of the thyroid having undergone curative thyroidectomy.

The first two subjects, brother and sister, were an 11-year-old boy and a 12-year-old girl with a family history: a mother with NEM2A operated in 2003 for CMT, an aunt also Family CMT, another aunt who died of thyroid cancer, and one uncle and cousins with NEM2A but not yet undergoing surgery.

The history of the disease in these 2 children dates back to April 2008 as part of a routine screening of family CMT after confirming their NEM2A

involvement. Clinical examination was normal with clinical euthyroidism. The genetic analysis reveals the presence of a C634Y gene mutation of the proto-oncogene RET, at the level of exon 11.

Biological assessments (thyroid, calcitonin, parathyroid) returned normal. Cervical ultrasound showing a normal-looking thyroid gland with inter-jugulo-carotid ADP presence. Both patients underwent total thyroidectomy with hormone replacement therapy.

Anatomo-pathological study showing C cell hyperplasia with a negative calcitonin immuno-labeling. The third patient was a 10-year-old boy with a history of treatment-treated tonsillitis, and family with thyroid cancer in an operated aunt.

The history of his illness going back 3 years before his admission by the progressive installation of dyspnea with exertion with cough, by dysphagia initially with the solids, and then with the liquids with a evolution of the disease in a context of unencrypted weight loss, general deterioration and apyrexia.

The evolution was marked 2 days before his hospitalization by the installation of total aphagia for which he was admitted for a possible treatment. The objective clinical examination shows a child in poor general condition, asthenic with slightly discolored conjunctiva and a weight loss of -2 D.S.

The cervical examination shows a lateralized cervical mass on the left very painful. Clinical exploration of body measurements, consistency, and mass mobility in relation to the deep and shallow plane has not been established due to pain. Examination of peripheral lymph nodes was normal.

The child had a OGD Transit initially showing superior esophageal stenosis probably related to extrinsic compression. Tracheal fibroscopy demonstrated 80% tracheal lumen stenosis in relation to extrinsic compression of the glottis.

Cervico-thoracic CT shows a malignant process of the left thyroid lobe. A Thyroid CT scintigraphy shows a left lobe of regular contours, homogeneous fixation with the presence of a cold nodule taking the entire left lobe of the thyroid.

MDP-CT bone scintigraphy revealed a normal and symmetrical fixation of the tracer on the entire skeleton, confirming the absence of arguments in favor of secondary locations.

The child had a total thyroidectomy with simple operative follow-up (disappearance of aphagia and dyspnea) and hormone replacement therapy. The pathological study confirms a medullary thyroid cancer with a postoperative assessment made of calcitonin high income more than 70 times normal. A family survey was in progress but our patient is lost of sight.

DISCUSSION

Medullary thyroid carcinoma (MTC) is a rare cancer that develops at the expense of the thyroidal C-cells responsible for the secretion of calcitonin (CT).

The characteristics of familial medullary thyroid cancer being [1]: early age, sex ratio = 1, familial ATCD of cancer or thyroid nodule (multi-nodular goitre), familial ATCD of other endocrine lesions (pheochromocytoma) or non-endocrine, multi-focus, bilaterality as well as C-cell hyperplasia.

CMT accounts for 5-10% of thyroid cancers. Its incidence in nodular thyroid pathology is around 1-2% [2,3]. The CMT can be revealed by a thyroid nodule with euthyroidism or a multi-nodular goitre, most often associated with satellite lymphadenopathies: a high preoperative CT allows to confirm the diagnosis.

It occurs in two forms: sporadic majority and familial in nearly 30% of cases [4]: it then becomes part of multiple endocrine neoplasia type 2, a hereditary monogenic disorder related to germ mutations of the RET gene, genetic marker of the CMT [5].

The sporadic case is more common among adults with an average age of 50 years. In contrast, the familial form occurs quite often in the pediatric population before 20 years on average [1,3], especially in the context of the Sipple syndrome (NEM 2A) similar to the two cases in our study, or Gorlin syndrome. (NEM2B). The CMT is constant before the age of 10 years in the children carrying NEM2A, the CMT appears later than in the carriers of NEM2B. Indeed, in the carriers of NEM2B, the CMT is constant before the age of 2 years [6].

The CMT has a biological specificity by the secretion of calcitonin (CT), which is the tumor biological marker for diagnosis and follow-up [7].

Early diagnosis, even infra-clinical diagnosis, can be done by the systematic determination of CT in nodular thyroid pathology, which allows surgery adapted to an early anatomo-clinical stage, the only guarantors of a cure [8,9]. The systematic analysis of the RET gene before any CMT makes it possible to diagnose a familial form, to allow pre-symptomatic diagnosis, and the specific and early management of genetically at-risk relatives.

The management of advanced and / or metastatic CMT should, in the near future, be able to benefit from therapies based on the use of peptides and new radiolabeled analogues, and new molecules

targeted on the signaling pathways of the RET oncogene, including tyrosine kinase inhibitors.

Most recently used is the Pentagastrin Stimulation Test, which consists of a slow IV injection of 0.5 µg / kg of a synthetic gastrin analogue with blood samples taken before injection and at one, three, five and ten minutes. after the start of the injection. It allows to confirm the diagnosis of pathology of C cells (CMT or HCC), it is useless if the basal CT value is very high (> 100 pg / ml) with a diagnosis of CMT highly likely on clinical or cytological arguments. In CMT, the stimulated CT peak is greater than 100 pg / ml [10].

The prognosis of CMT is essentially related to the anatomo-clinical stage and the quality of the initial surgical excision. All patients diagnosed with CMT should undergo total thyroidectomy with central compartment lymphadenectomy. It has been shown that up to 45% of patients have metastatic deposits in the central compartment and the excision of these lymphatic nodes at the first procedure can significantly reduce the recurrence rate.

Preoperative serum basal serum calcitonin is also useful in determining the extent of lymph node metastasis. Ten-year survival rates are as high as 80% for patients not biologically recovered by surgery and more than 95% at 10 years for those who are postoperatively [1, 2, 5, 11-13].

CONCLUSION

Medullary thyroid cancer, although rare in children, is characterized by a significant familial component compared to other types of thyroid cancer. It should be emphasized that this is part of multiple endocrine neoplasia type 2.

Prophylactic surgery for medullary thyroid cancer is an almost unique example of the possibility of preventing cancer in a genetically determined pathology. It is based on the good genotype-phenotype correlation associated with a very strong penetrance of the familial CMT mutation.

The contribution of genetics makes it possible to better target the operative indications of medullary carcinoma of the thyroid. In addition, the genetic study of these familial cancers makes it possible to carry out a family survey, which makes it possible to detect early and thus greatly improve the vital prognosis in the subject affected by the mutation concerned, responsible for familial cancer.

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