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Medullary Thyroid Carcinoma in Algeria: Phenotypic And Genotypic Characteristics

NS Fedala[1], Fetta Amel Yaker[2], Ali El Mahdi Haddam[3], Nadia Kalafat[4], Lydia Lounis[5],
Bab El Oued Hospital, Algeria

Abstract: *A comparative study was conducted between sporadic CMT (CMTS , n : 19) and heritable (CMT H , n = 22) integrated within a MEN2A . The diagnosis of CMT in CMTH group was made rather than the CMTS group It was revealed by a thyroid nodule in CMTS and family screening in CMTH . the CMTH were stage I TNM in 78.9 %, while the CMTS is almost equally divided between stage II (26.31%) I and IV (21.05 %) . Genotypically , two mutations were observed 634 mutation and618 RET gene mutation . A genotype-phenotype correlation was observed*

Keywords: *medullary thyroid carcinoma, MEN2A , RET protooncogene , genotype- phenotype*

I. Introduction

Medullary thyroid carcinoma (MTC) is a rare thyroid cancer. It represents 8-10 % of them.[1] It takes origin from the thyroid parafollicular cells which product the calcitonin (TCT). TCT assay permit the diagnosis and monitoring of this neoplasia . CMT is sporadic 75 % of cases, and hereditary as an autosomal dependent disorder in 25 % of cases integrated in the context of familial MTC or MEN 2.[2] The prognosis of this cancer differs according to the one or the other form. Sporadic CMT has a worst prognosis. It's characterized by a higher degree of evolutivity due to a later diagnosis and a more advanced tumor stage.[3] Genomic mutations responsible of familial forms are known, they are due to a RET gene mutation localized on chromosome 10[4] Systematic research of this mutation in any CMT case permits a pre symptomatic diagnosis and also a prophylactic effective support in the patients with a genetically related risk The aim of this study was to investigate the clinical and evolutionary characteristics of sporadic medullary thyroid cancer (MTCS)and hereditary(HMTC) and establish genotype phenotype correlations

II. Materials And Methods

It is a descriptive and comparative study between two groups of patients :HMTC and MTCS. All patients had a clinical examination , a TCT dosage and a thyroid cytopunction. The diagnosis of CMT was confirmed after pathological and immunohistochemical study . The exploration was completed by a genetic mutation of the RET gene research and a guided extension work-up . Tumor staging was done according to the TNM classification

III. Results

41 MTC patients were reviewed . 46.3 % were sporadic and 53.6 % hereditary integrated in MEN2A syndrome(n : 5 families) .Age of discovery was significantly earlier in HMTC group Revelation mode of sporadic MTC is, in all cases, a thyroid nodule, while in heritable CMT , the circumstances of diagnosis were a systematic family screening (42.8 %), the presence of pheochromocytoma (33.3 %) and a thyroid nodule (25 %). The sporadic MTC are uni nodular in all cases while the HMCT are mostly multi- nodular (81%). Biologically, the TCT average was about 1926.42 ±pg / higher in sporadic group but not statistically significant . In these ones , the TCT was normal in 6% of patients. the thyroid cytopunction has contributed in 73.3 % of sporadic case and 50%of the inherited ones. The pathologic stage was significantly less advanced in the HMTC, metastasis were more frequent in sporadic forms and affected several organs while in the hereditary MTC , we note only lymphadenopathy(TABLE I)

The postoperative evolution was marked by a remission in 26.82% and only in hereditary forms.

Genetically, two RET gene mutations were observed, it was the 634's mutation (Fig. 1) and the 618's one . A genotype-phenotype correlation was observed (Table II)

IV. Discussion

MTC is a rare cancer. It is characterized by the production of TCT which is a diagnostic and prognostic marker and by the existence of genomic mutations of RET gene on chromosome 10 responsible for inheritable familial forms.[2] Sporadic forms are predominant . the insignificant difference in number of patients between the

two groups in our study may be explained by a limited sample. The fortuitous discovery of MTCS tumors make them have a worst prognosis with a higher degree of evolutivity is due to a later diagnosis and more advanced tumor stage .A Diagnosis and an earlier treatment of hereditary forms is largely due to systematic screening , especially in familial forms.[5] Indeed, elements predicting a good prognosis are essentially the young age, the TNM stage and the quality of surgery.[5,6] The first-line treatment of MTC is surgical and the quality of initial management is important elements of prognosis. When the diagnosis is known preoperatively and the tumor stage is not advanced, total thyroidectomy complemented by a set of lymph node

Dissection touching the lateral and central compartiments permit to obtain a post operative remission.[7] The total thyroidectomy should be done knowing that the lesions are constantly bilateral in familial forms and in a third of apparently sporadic forms.[8] Dissection of lymph node compartments must be larger regardless of preoperative exploration an size of injury because lymphadenopathy are very common: over 50% in macro cancers and 30.9 % in micro cancers.[9,10] The circumstances of diagnosis of CMT are different depending on whether it is a sporadic form, index case of a familial form or detected by a familial screening. Exploration of thyroid nodule is a usual mode of revelation of MTCS and index case of familial forms.[8]

The fine-needle nodule cytopunction , necessary in front of any cold thyroid nodule permit sometimes to do the diagnosis when it's realized by an experienced pathologist . However, the determination of TCT rate is the only certain way to make the preoperative diagnosis . The debate is not closed on the need for routine this assay in any thyroid nodule . MTC are rare and the problem of cost / effectiveness ratio. Profitabilityof TCT dosage is low (1 % or less) but compared with the cost of reoperations required if the preoperative diagnosis is not made or that of the management of advanced and metastatic tumor, many authors advocate screening systematic.[11]. It should be noted that the base CT may be normal in case of small tumor or C-cell hyperplasia in the context of H MTC . In these cases , an assessment of the basic rate of CT and under pentagastrin stimulation remains useful because of possible dissociation between the genetic status and expression of the disease.[11,12] In fact, the TCT rate is correlated with tumor size. More advanced the malignancy stage is, higher is the rate which is observed in sporadic forms.[11]

In its hereditary form, and whatever its phenotypic expression, MTC is associated with punctual mutations in RET proto-oncogene , altering the structure and activity of the RET protein, a membrane receptor group of receivers with seven transmembran domains with tyrosine kinase activity.[13,14]

Some of them are located in the coding region for the rich extracellular portion of the cystein receptor and are described as a mutation affecting receptor activity and able to maintain it in an active state. others, located in the region encoding for the tyrosine kinase domains of the receptor, interfere with activation of intracellular process . Among the mutations described, some seem crucial to induce the disease phenotype. This is particularly observed in the MEN 2.[14] More than 95 % mutations present in families are on the codon 634 of exon 11. The consequence is that a patient carrying this mutation has a high risk of developping MEN 2a . Some other cases have mutations in 618 codon or 620 on exon 10.[15] The existence of a genotype-phenotype relationship is well established and used.[16] Some types of mutations are predictive to development of pheochromocytoma or hyperparathyroidism,[16] the aggressiveness of MTC and early malignant transformation of cells hyperplasia C : very early in patients mutation in exon 11 for MEN 2a with early expression or slower in some forms of F- MTC with a mutation in exon 10.[16]

In the absence of effective surgical treatments, identification of RET mutation and family screening in hereditary forms of the disease can help to manage more effectively the disease and improve the prognosis of patients

V. Conclusion

MTC whether sporadic or hereditary, is a rare disease. Its prognosis depends essentially of tumor's stage and the quality of the initial surgical treatment. TCT dosing and genetic analysis of RET gene mutation are essential to establish an early diagnosis in CMT patients . The existence of a genotype-phenotype correlation can be used to ensure a better prognosis

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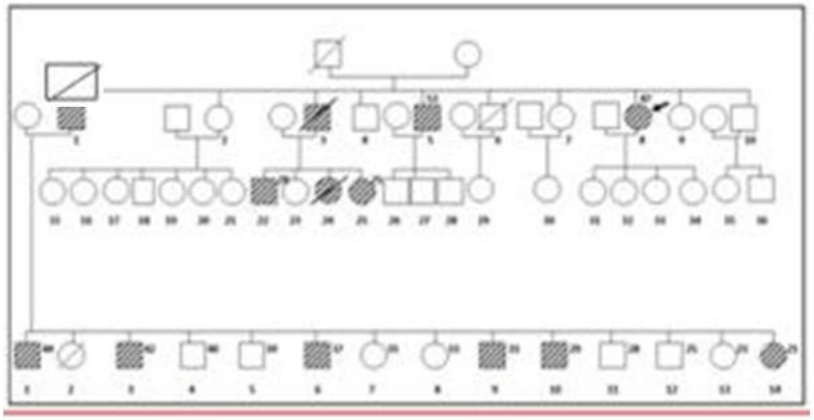
Figures



Members screened

E3 The members and detected mutation carriers Member died
Tables

Table I: phenotypic characteristics in MTC(CMCT and HMCT)

Phenotypic characteristics	CMCT	HMCT	P
Age of discovery (years)	**47.1 ± 12.8**	**33.4 years ± 12.5**	DS
Sex-ratio (H/F)	0.11	0.83	DS
Median tumor size (cm)	34	28	DNS
Thyrocalcitonine (pg/ml)	2884,75	968,1	DNS
TNM stage			
T1%	21,05	78,94	
T2%	26,31	0	DS
T3%	21 ,05	0	
T4%	52,63	0	
Metastasis	26.3	18,18	
Lymph node %	31.6	18.2	DS
bone %	15.8	0	
lung %	5.6	0	
liver %		0	

Table II: Phenotypic Characteristics of subjects RET +.

Famille	Patient	Gender	Age (Years)	Age at diagnos is	Reason for consult ation	Additional events
A	**II.8 (index)**	**F**	**47**	**36**	**PCC**	**MTC + HPT**
	II.1	**H**	**65**	**55**	**FAMI SUR LYVEY**	**MTC+PCC+**
	II.5	**H**	**53**	**42**		**MTC+PCC+**
	III.1	**H**	**44**	**34**		**MTC+PCC+**
	III.3	**H**	**42**	**34**		**MTC+PCC+**
	III.6	**H**	**37**	**26**		**MTC+PCC+**
	III.9	**H**	**31**	**22**		**MTC+PCC+ HPT**
	III.10	**H**	**29**	**23**		**MTC+PCC+**
	III.14	**F**	**21**	**19**		**MTC+PCC+**
	III.22	**H**	**28**	**26**		**MTC+PCC+ HPT**
	III.25	**F**	**21**	**13**		**MTC+PCC+**
B	**II.3 (index)**	**F**	**50**	**44**	**PCC**	**MTC+HPT**
	II.7	**F**	**40**	**37**	**Family survey**	**MTC +PCC**
	II.8	**F**	**38**	**35**		**MTC +PCC + HPT**

MTC

	I.1	**F**	**40**	**37**	**Family**	
C	**II.1**	**M**	**25**	**24**	**survey**	**PCC+ HPT**
	II.2	**M**	**18**	**18**	**Family**	
					survey	
D	**I.1**	**F**	**38**	**28**	**PCC**	**MTC+H PT**
	II.1	**H**	**28**	**27**	**Family**	

survey
Family
survey

Mtc

	1.1	**M**	**36**	**35**	**Family**
E	**II.2**	**F**	**30**	**30**	**survey PCC+ HPT**
	II.3	**M**	**22**	**21**	**Family**

survey