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Research Paper

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## Recessive Expression of Dermatological Lesions, Adrenocortical and Thyroid Tumors in MEN1 Syndrome: Study Done in Algeria

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### ABSTRACT:

**Objective:** Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant inherited syndrome; the heterozygous mutated allele is transmitted by the affected parent, regardless of gender. Some lesions are found with recessive inheritance in Algerian patients. This made us look for and study families with recessive tumors. **Methods:** We systematically gathered all cases of familial Multiple Endocrine Neoplasia Type 1 (MEN1) and conducted comprehensive biological and technical analyses, which included detailed inquiries into personal and familial medical histories. We meticulously tracked and investigated the transmission patterns of each lesion, following their progression from the first generation to subsequent generations. **Results:** In our research, we observed that only 4 types of tumors were predominantly inherited in a dominant fashion. Conversely, the majority of the other tumors and lesions associated with MEN1 exhibited a significantly recessive inheritance pattern. **Conclusion:** Upon observing that certain tumors were inherited from grandparents to grandchildren, skipping the parental generation (and this was in several families that were studied; especially since some families had a blood-related marriage), we raised the possibility of the presence of recessive traits in this syndrome, although in general it is dominant.

**Keywords:** MEN1, generation, dominant, recessive.

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## 1. Introduction

Multiple endocrine neoplasia type 1 (MEN1) is a main hereditary syndrome predisposing to endocrine tumors, including gene MEN1, which is currently accessible to techniques of diagnosis and functional studies. Beyond a veritable revolution in patient care, research into the pathophysiological mechanisms of the development of these tumors has developed strongly in this autosomal dominant hereditary disease who's with high penetrance (1). MEN1 (Wermer's syndrome) is mainly characterized by damage to the parathyroid glands causing hyperparathyroidism (HPT), and by the occurrence of duodenopancreatic tumors and pituitary adenomas (2). Additionally, several other organs can be affected by MEN1; thus there are carcinoids (3, 4) located in the bronchi or thymus, tumors of the adrenal cortex (mainly non-functional), skin lesions (5) (angiofibromas of the face, lipomas), as well as tumors of the central nervous system (meningiomas, ependymomas) (6).

The familial form corresponds to a case of MEN1 having at least one first-degree relative affected by one of the characteristic endocrine tumours (7). Several mutations are observed on one allele of the MEN1 gene, but in more than 80% of these tumors, the second allele of the MEN1 gene is altered or most often deleted due to a loss of heterozygosity (LOH) (8), a deletion probably linked to the fact that the cell carrying the mutation on the first allele is already undergoing a certain process of chromosomal instability (1).

## 2. Materials and methods

During a study of the MEN1 syndrome of 6 years of research, which was done in the laboratory of the University Hospital of Constantine (Algeria), 20 cases of family MEN1 were found.

### **The clinical diagnosis of MEN1 is based on:**

- The presence in the same patient of at least two of the five cardinal lesions which are tumoral involvement of the parathyroids, the endocrine pancreas, the anterior pituitary, the adrenal glands, and the thymic or bronchial endocrine tissue (9)
- HPT in young subjects (less than 50 years old) (10).
- Either the existence of a known isolated attack of the disease, cardinal or not (parathyroid, pancreas, pituitary, adrenal glands, thymus, bronchi, tumor of the central nervous system), associated with a gene mutation of the MEN1 gene (11).
- The typical familial form shows in at least two first-degree relatives the existence of at least one of the cardinal lesions of MEN1. Are excluded from this definition, single-organ endocrine genetic diseases linked to another genetic syndrome such as familial pituitary attacks, familial hyperparathyroidism (12).

### **Biological and radiological diagnosis:**

Hormonal assay from patient serum (Whole blood samples for the genetic study were taken at the bend of the elbow).

- twenty four hours calciuria is an important test to differentiate primary hyperparathyroidism from hypercalcemic -hypocalciuric syndrome (13).
- Look for functional impairment (ZES, insulinoma, glucagonoma, etc.) by questioning, examination and biology.
- Echoendoscopy, echography or scanner. Under study, the replacement of echoendoscopy by MRI.
- A questionnaire for MEN1 patients was drafted, comprising three parts:

part 1: marital status, part 2: personal history, part 3: family history.

### 3. Results

Our study involved 14 women (70%) and 6 men (30%) who presented with familial MEN1, with an age ranging from 20 to 53 years. We only collected patients with a clear family history of the disease (we found 13 cases and the rest of the patients (7 patients) had no clear pathological information about their family history). 100% of the 13 cases have a first exploration at a very young age (mean age 25 year). We divided them and their families according to tumor types (Table1).

Table 1. Distribution of MEN1 patients and their 1st degree relatives according to the type of lesion

| <b>lesion</b>               | <b>Patient Frequencies</b> | <b>1st degree relative frequencies</b> |
|-----------------------------|----------------------------|----------------------------------------|
| Primary hyperparathyroidism | 70%                        | 50%                                    |
| Thyroid tumor               | 20%                        | 20%                                    |
| Adrenocortical tumor        | 10%                        | 10%                                    |
| Duodeno-pancreatic tumor    | 5%                         | 5%                                     |
| Pituitary tumors            | 10%                        | 5%                                     |
| Pheochromocytoma            | 10%                        | 10%                                    |
| Testicular tumors           | 15%                        | 15%                                    |
| Breast tumors               | 10%                        | 10%                                    |
| Liver tumors                | 5%                         | 0%                                     |
| Dermatological lesion       | 10%                        | 10%                                    |
| Lung injury                 | 10%                        | 15%                                    |

During the study of familial MEN1, it was noticed that the transmission of endocrine and exocrine lesions (such a dermatological lesion) is sometimes recessive (Table 2); however, MEN1 is known to be an autosomal dominant syndrome. This is why we studied all families with MEN1. We considered the transmission of a lesion to be recessive when: a lesion which appears in one of the parents, then disappears in the second generation, then reappears in the third generation or a lesion appears in the 2nd generation and does not exist in the 1st generation which contains other MEN1 lesions.

The table presents a detailed analysis of the transmission patterns of various lesions in Multiple Endocrine Neoplasia Type 1 (MEN1). It highlights the proportions of dominant and recessive inheritance for different tumor types.

Primary hyperparathyroidism, Pheochromocytoma, pituitary tumors and lung tumor have a predominant transmission pattern.

While thyroid tumors, adrenocortical tumor, breast tumors , testicular tumors , duodeno-pancreatic tumors, Liver tumors, and dermatological lesion are recessive in 100% of our cases .

Some tumors are transmitted together as they are from the first generation to the second generation in families (Table 3). As we saw in the table that The HPT + breast tumor were transmitted in a related manner. For example: one family suffers from MEN1 syndrome, and each case contains a group of tumors different from the other cases, but we noticed that (HPT + breast tumor) that was present in the mother was transmitted directly to one of her daughters.

We noticed in other family the transmission of (HPT + thyroid tumor) from the mother to one of her daughters and to one of her granddaughters from another daughter who does not have the syndrome.

Table 2. The lesions and the way of their transmissions (phenotypic study):

| Lesion                   | Dominant | Recessive |
|--------------------------|----------|-----------|
| HPT                      | 100%     | 0%        |
| Thyroid tumor            | 0%       | 100%      |
| Adrenocortical tumor     | 0%       | 100%      |
| Pheochromocytoma         | 100%     | 0%        |
| Breast tumors            | 0%       | 100%      |
| Testicular tumors        | 0%       | 100%      |
| Lung tumor               | 100%     | 0%        |
| Pituitary tumors         | 100%     | 0%        |
| Duodeno-pancreatic tumor | 0%       | 100%      |
| Liver tumors             | 0%       | 100%      |
| Dermatological lesion    | 0%       | 100%      |

Table 3. Transmission of some tumors in a related dominant manner from one generation to another (in tow families)

| 1st degree relative | Patient             |
|---------------------|---------------------|
| HPT + thyroid tumor | HPT + thyroid tumor |
| HPT + breast tumor  | HPT + breast tumor  |

#### 4. Discussion and Conclusion

We noticed that all patients with familial MEN1 had their first symptoms at an early age (<20 years in some patients) and most had HPT as their first symptom. Some lesions are transmitted mainly from parent to son, such as (HPTp, pheochromocytoma, lung tumor, and pituitary tumor) (Table 2). Some other lesions were observed in grandparents and grandchildren, but they did not appear in parents, while other lesions were observed in them. So they were transmitted recessively as Thyroid tumors, adrenocortical tumors, breast tumors, testicular tumors, liver tumors, duodenal and pancreatic tumors, and skin lesions.

This leads us to develop the hypothesis of the presence of recessive tumors in multiple endocrine neoplasia type 1, whereas it was previously considered to be an autosomal dominant disease. These results support what authors Duval, M., & Haissaguerre published in 2023, and also add new and detailed information about recessive traits in MEN1 syndrome.

Tumors were transmitted in a related manner from the first generation to the second generation ( HPT + breast tumor) may also indicate that there is a dominant transmission of association between some tumors (Table 3). And there is a recessive transmission of association of other tumors like the case of ( HPT + Thyroide tumor ). (Table3)

In our research, we collected DNA from a group of patients, but for many of the patients' relatives we were unable to collect their DNA due to their death. I hope that there will be genetic research on new families in which most of their members are still alive to further support these results.

Finally, knowing the existence of recessive traits in this syndrome calls us to encourage non-marriage of relatives who belong to the family of a patient with this syndrome.

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