

One genotype with a myriad of phenotypes: A family with multiple endocrine neoplasia

Oumeyma TRIMECHE¹, Fatma MNIF¹, Fatma ABDELHEDI², Kaouthar El ARBI¹, Yosra LAJMI², Nadia CHARFI¹, Mouna MNIF¹, Faten Hadj KACEM¹, Dhousha Ben SALAH¹, Khoulood BOUJELBENE¹, Mohammed ABID¹, Mouna ELLEUCH¹, Nebila REKIK¹

¹Endocrinology Department, Hedi Chaker University Hospital, Sfax, Tunisia; ²Genetics Department, Hedi Chaker University Hospital, Sfax, Tunisia

E-mail: trimeche.oumeymaa@gmail.com

Objective. Multiple endocrine neoplasia type 1 (MEN1) is a very rare genetic disorder characterized by an autosomal dominant inheritance. We aim through this case series to delineate the wide spectrum of its clinical features.

Methods. In the present study, we report the clinical and genetic findings of four siblings affected by this disorder. DNA was extracted from patients' blood leukocytes using a phenol-chloroform method and assessed for purity with a NanoDrop spectrophotometer. Ten exons of the *MEN1* gene were amplified by PCR, verified by gel electrophoresis, and sequenced using Big Dye Terminator chemistry followed by capillary electrophoresis. The sequences were then analyzed with CHROMAS and compared to reference sequences. As for the variant, interpretation and pathogenicity were assessed using Ensembl, ClinVar, dbSNP, gnomAD, Alamut Visual, and VARSOME.

Results. We highlight the wide range of phenotypes encompassing primary hyperparathyroidism, macroprolactinoma, lipomas, papillary thyroid carcinoma, ectopic thyroid, multinodular goiter, and bilateral adrenal nodules observed in this family contrasting with the same pathogenic frameshift mutation. We also pinpoint to a second mutation detected in two of the siblings while discussing its pathogenicity. Finally, we provide an overview of the clinical manifestations of MEN1 and its genetic background.

Conclusion. This research sets the stage to further investigate the molecular mechanisms underlying the novel nonsense mutation. Additionally, it incites other research to explore the frequency of this mutation in other populations and finally to conduct functional studies.

Keywords: multiple endocrine neoplasia, papillary thyroid cancer, ectopic thyroid, genetics

Multiple endocrine neoplasia type 1 (MEN1) also known as Wermer's syndrome is a very rare genetic disorder characterized by an autosomal dominant inheritance. The clinical spectrum of this syndrome is quite broad; however, some conditions are particularly frequent in MEN1 such as primary hyperparathyroidism (PHP) present in more than 90% of cases, duodenopancreatic neuroendocrine tumors (DPNETs) affecting 55 to 70% of patients, and pituitary adenomas (PA) found in approximately

40% of MEN1 genetic defect carriers (Al-Salameh et al. 2021). Recognizing MEN1 is critical, since the diagnosis of this syndrome may alter the therapeutic approach as well as the follow-up of these patients. To date, no clear genotype-phenotype has been established (Kamilaris and Stratakis 2019). Aiming to highlight this lack of correlation and the diverse features related to this condition, we report a family diagnosed with MEN1 depicting the varying phenotype each member had.

Materials and Methods

Subjects. Clinical, laboratory, and radiological findings were extracted from our patients' medical charts. Written informed consent was obtained from all participating family members prior to sample collection and genetic analysis. All data were anonymized to ensure participant confidentiality.

DNA extraction and quality verification. DNA was extracted from patients' peripheral blood leukocytes using a phenol-chloroform method and assessed for purity with a NanoDrop 2000c spectrophotometer.

PCR amplification. Ten exons of the *MEN1* gene were amplified by PCR using a ready to use solution (Master Mix PCR, Thermo Scientific™ DreamTaq Green PCR), containing Taq polymerase, dNTP, magnesium chloride and buffer solution. Touchdown PCR was thereafter used as amplification program and quality control of PCR was verified via gel electrophoresis (2%).

Sequencing procedure. In order to conduct a sequence reaction, a Big Dye Terminator v3.1 (Thermo Fisher Scientific/ Applied Biosystems), comprising Taq polymerase, dNTPs, marked dNTPs, magnesium chloride and buffer solution. Unincorporated dNTP and ddNTP were eliminated applying the ethanol precipitation method. A two-step strategy using "Applied Biosystems3500", an 8-capillary electrophoresis, was employed. First, the final products were separated based on their sizes, using a highly resolving gel. The second step consisted of identifying the base by laser application. Subsequently, "CHROMAS" was used to read the sequences, which appeared as electropherogram peaks. Finally, the patients' sequences were compared with *MEN1* reference sequence, provided by the BLAST tool.

Bioinformatics tools. The Ensembl genomic database was utilized for DNA sequence, and protein search (Wautot et al. 2002). The transcript NM_130799.2 on the human genome version 37 was selected. The following databases were consulted for variant interpretation: ClinVar, dbSNP and gnomAD. For pathogenicity prediction and phylogenetics, Alamut Visual software version 2.11 was employed. The American college of medical genetics classification of variants was obtained through the VARSOME software.

Results

The epidemiological, clinical and genetic characteristics of the patients are summarized in Table 1.

Case 1

A 31-year-old woman (M.M.) who was referred to our Department of Endocrinology for pituitary incidentaloma and secondary amenorrhea for 6 months. Two months before her referral, an MRI of the facial skeleton was conducted aiming to characterize a painless left maxillary mass. It revealed the presence of a left osteolytic tumoral process of 4.5 cm diameter, which was then diagnosed on account of anatomopathological exam as a maxillary epulis. The MRI also unraveled the presence of a PA with a suprasellar extension (34*25*21 mm) abutting the optic chiasm (Figure 1). Owing to the elevated prolactin level (1544.11 ng/ml; >200 ng/ml), the diagnosis of macroprolactinoma was made and biochemical evaluation of the anterior pituitary axis revealed an insufficiency of the gonadotropic, somatotrophic, thyrotrophic, and corticotrophic axis.

The patient was treated initially with bromocriptin and substitutive doses of l-thyroxine and hydrocortisone. Albeit appropriate dosage and therapeutic compliance, prolactin level persisted elevated suggesting a resistance to dopaminergic agonists. Thus, a transsphenoidal surgery was conducted, which resulted in a reduction of the pituitary mass to 28*24 mm and the reduction of prolactin level to 158 ng/ml. She was subsequently treated with cabergoline.

Owing to the young age of our patient, a screening for genetic diseases was carried out, which unveiled the presence of PHP complicated with severe osteoporosis and bilateral renal lithiasis. Additionally, she had a multinodular goiter with negative immunological study and normal calcitonin. The association of PA and PHP led us to retain the diagnosis of *MEN1*. She underwent a subtotal parathyroidectomy and concomitant total thyroidectomy. Intriguingly, the epulis vanished in days. Otherwise, no DPNETs nor adrenal tumors were found on thoracoabdominopelvic CT scan. Nevertheless, a gigantic 14 cm long intra-abdominal lipoma was incidentally discovered (Figure 2). Since she had an aggravation of her visual function despite optimal doses of cabergoline, she was referred for pituitary surgery again. She died on the operating table due to a carotid lesion.

Case 2

The female patient (Z.N.) was first assigned to our Department of Endocrinology for severe refractory hypocalcemia post total thyroidectomy. She had a past medical history notable of hypothyroidism

Table 1
Phenotype and genotype of our patients

Variable	Case 1 (M.M.)	Case 2 (Z.N.)	Case 3 (W.M.)	Case 4 (F.Z.)
Age at diagnosis	31 years	48 years	48 years	48 years
Gender	Female	Female	Male	Female
Primary lesion of MEN1	Pituitary adenoma	PHP	PHP	PHP
Associated lesions	PHP Intraabdominal Lipoma Multinodular goiter	Hypothyroidism Ectopic thyroid gland Leiomyoma	Hypothyroidism Multinodular goiter	PTC Bilateral adrenal nodules Pulmonary nodules
Complications of PHP	Severe osteoporosis Bilateral renal lithiasis	Osteopenia	Osteopenia Bilateral renal lithiasis	Severe osteoporosis
Preoperative calcemia (mmol/l)	2.68 to 2.77	N.A.	2.66	3.17
Preoperative phosphoremia (mmol/l)	0.74 to 0.92	N.A.	0.46 to 0.68	0.7
Preoperative PTH (mmol/l)	395	N.A.	67.5 to 76	400.1
Calciuria (mmol/24h)	9.9	N.A.	3.72	3.8
Outcome	Resistance to DA Death during pituitary surgery	Diabetes	Persistent PHP	N.A.
Genetic findings	NM_130799.2: c.689G>A p.Cys230Tyr	N.A.	NM_130799.2: c.689G>A p.Cys230Tyr	N.A.

NM_130799.2: c.1546dup(p.Arg516Profs*15)

Abbreviations: CPT - carcinoma papillary dopaminergic agonists; MEN1 - multiple endocrine neoplasia type 1; N.A. - not available; PHP - primary hyperparathyroidism; PTC - papillary thyroid carcinoma.

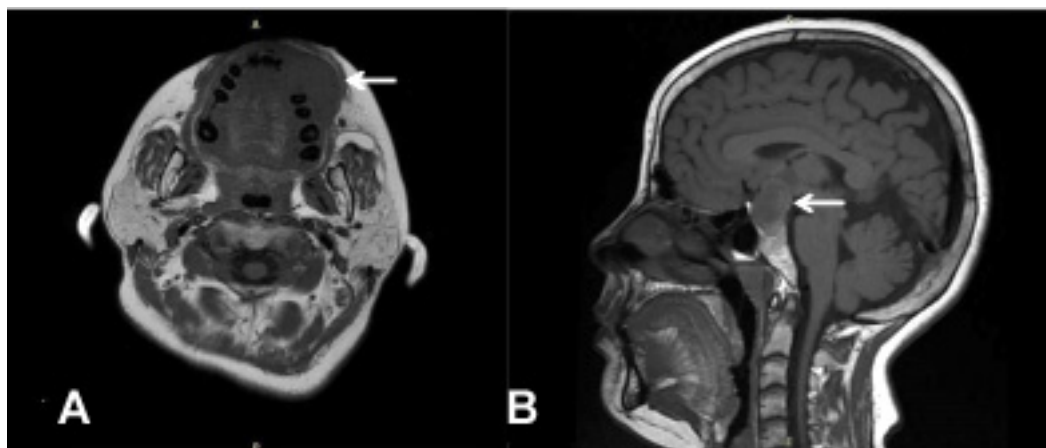


Figure 1. The presence of pituitary adenomas (PA) with a suprasellar extension abutting the optic chiasm unraveled by magnetic resonance imaging (MRI). Left maxillary tumor (A) and pituitary incidentaloma (B).

treated with L-thyroxine. During follow-up, her physician noted the presence of a right cervical mass. Cervical echography demonstrated the presence of a 4 cm right thyroid nodule associated with a 2 cm jugular lymphadenopathy. A total thyroidectomy with recurrent laryngeal nerve lymph node dissection was performed. To our biggest surprise,

the final pathological examination concluded to five parathyroid adenomas with the most voluminous measuring 6 cm and to a reactional lymphoid hyperplasia of the lymph nodes. Paradoxically, no thyroid tissue was found.

Upon her admission, she had a severe hypocalcemia, seven days post-surgery attributable to

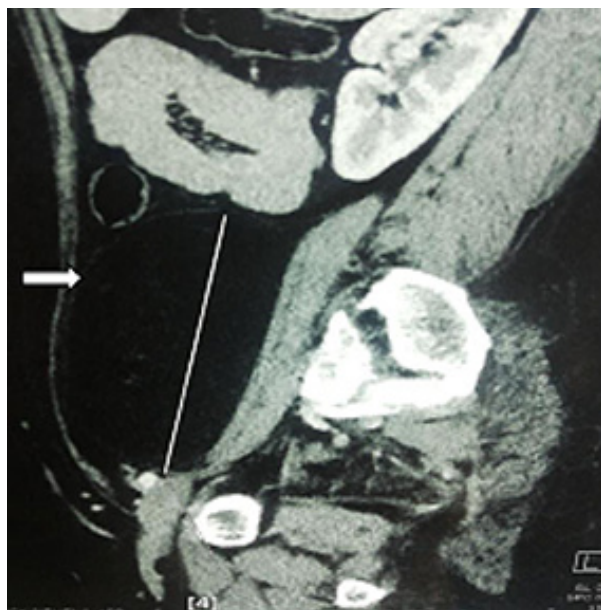


Figure 2. The presence of a gigantic 14 cm long intra-abdominal lipoma identified on a thoraco-abdominal-pelvic computerized tomography (CT) scan.

parathyroidectomy and aggravated by a hungry bone syndrome, which responded well to vitaminocalcic supplementation. As for her hypothyroidism and given her absence of thyroid tissue both on cervical echography and histological study, a thyroid scintigraphy was carried out, which revealed a lateral right minimal fixation aligned with the thyroid cartilage, which could correspond to thyroid tissue (Figure 3).

Given the patient family history of MEN1, thorough clinical, hormonal, and radiological exams concluded to the absence of secondary lesions. However, she was diagnosed with type 2 diabetes mellitus and is currently on metformin.

Case 3

The male patient (W.M.) was assigned to our Department of Endocrinology at the age of 46 years for persistent PHP. As for his medical history, he had bilateral and recurrent nephrolithiasis since the age of 31 years and hypertension treated with 10 mg of amlodipine. At the age of 41 years, he consulted for

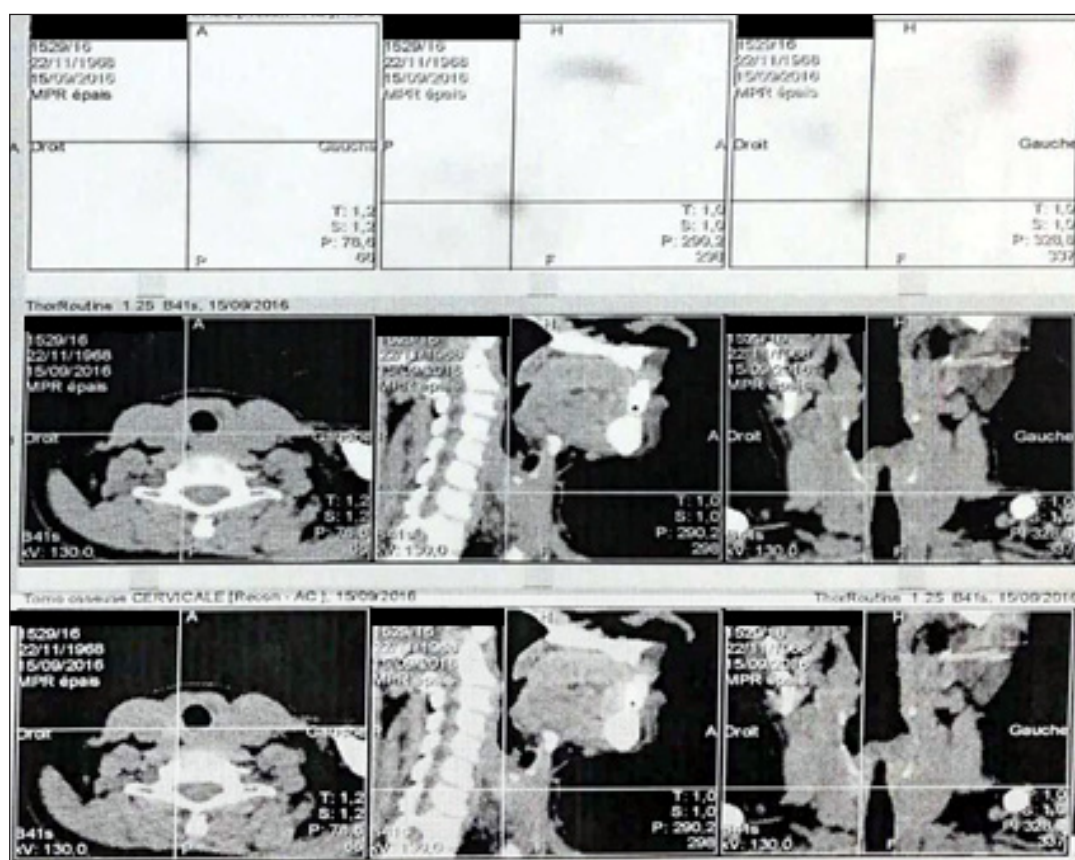


Figure 3. Lateral right minimal fixation aligned with the thyroid cartilage, which could correspond to thyroid tissue, as revealed by a thyroid scintigraphy and a computerized tomography (CT) scan.

infertility. An extensive clinical and paraclinical assessment dismissed hypogonadism as well as testicular abnormalities and unraveled an aberrant semen analysis (diminished volume, severe oligospermia, necrospermia, asthenozoospermia) as well as hypothyroidism.

On physical examination, he had a compressive goiter with signs of hypothyroidism. Given the presence of recurrent nephrolithiasis, a blood work-up was indicated and revealed PHP. He was then referred to surgery. At this point, his sisters were not yet diagnosed with MEN1. Concordantly to the preoperative findings, the patient had a total thyroidectomy and the removal of the two superior parathyroids.

The final pathological report concluded to a benign thyroid with a right superior parathyroid adenoma and a normal parathyroid tissue of the left superior gland. A persistent PHP was diagnosed. He had a resection of the parathyroid nodule detected by both cervical echography and scintigraphy as well as half of the remaining parathyroid gland. The immediate post-operative period was marked by a moderate hypocalcemia treated with prompt vitaminocalcic supplementation. Finally, aiming to screen for associated lesions, an exhaustive clinical, biological, and radiological assessment was carried out with normal results.

Case 4

A 48-year-old female patient (F.Z.) was referred to our Department of Endocrinology for PHP. She had a clinical symptomatology suggestive of hypercalcemia including abdominal pain, nausea, vomiting, asthenia, and weight loss for 7 months. A biological assessment showed severe hypercalcemia (3.17 mmol/l) with hypophosphatemia (0.7 mmol/l) and inappropriate PTH level (400.1 pg/ml). Cervical echography revealed a sub sternal oval left mass measuring 26*10 mm, suggestive of an ectopic parathyroid nodule associated with a thyroid nodule of 17*10 mm in the left thyroid lobe classified as EuTirads IV. MIBI scintigraphy displayed an intense fixation in retrosternal corresponding to the ectopic nodule seen in the echography.

Owing to the patient's family history and her genetic analysis, the diagnosis of MEN1 was retained. Thus, a panel of biological and radiological exams were effectuated unraveling the presence of two pulmonary nodules with benign radiological aspect and bilateral adrenal masses: the left measured 30*19 mm with a spontaneous density of 22 HU and an

absolute wash out of 51%, whereas the right adrenal gland harbored three adenomas of 13*10 mm, 11*11 mm, and 10*8 mm. Hormonal evaluation of the adrenal tumoral including plasmatic metanephrines and overnight dexamethasone suppression test were normal. She was assigned afterwards to surgery. The extemporaneous sample of the thyroid nodule disclosed a papillary carcinoma. Thus, she had a total thyroidectomy with recurrent laryngeal nerve dissection along with subtotal parathyroidectomy. Her recovery was uneventful.

Genetic findings. A heterozygous frameshift mutation of exon 10 of the *MEN1* gene was depicted in all our patients: NM_130799.2: c.1546dup (p.Arg516Profs*15). Additionally, a novel nonsense heterozygous mutation: NM_130799.2:c.689G>A (p.Cys230Tyr) was spotted in the cases 1 and 3.

Discussion

This case series sheds light on the wide phenotypic features of MEN1 including possibly thyroid ectopy and papillary thyroid carcinoma. It also underlies the eventuality of two concomitant mutations of the *MEN1* gene and highlights the occurrence of novel nonsense mutation.

As cited above, MEN1 is a very rare syndrome attributable to inactivating mutations of the *MEN1* gene located on the chromosome 11. More than 1000 mutations have been found in the literature with no particular hot spot (Kamilaris and Stratakis 2019).

Germinal mutations of *MEN1* gene are dominated by frameshift (41%) followed by nonsense (23%) and missense mutations (20%) (Wautot et al. 2002; Falchetti 2017). The frameshift mutation observed in our patients is a pathogenic variant, which is corroborated by its segregation within this family. Its appearance in other MEN1 cases (Marx et al. 1998; Kytola et al. 2001; Pieterman et al. 2012) and its extremely rare occurrence in the normal population according to gnomAD. Additionally, functional studies of the resulting protein highlight its altered nuclear localization. However, the pathogenicity of the nonsense mutation c.689G>A needs to be ascertained. Some arguments are in favor of this hypothesis: its absence in gnomAD, the implication of highly conserved amino acid, and its probable deleterious effect based on *in silico* prediction tools. Both functional studies and probing of this mutation in Tunisian healthy individuals are required to classify this novel finding.

As demonstrated above in our case studies and despite all siblings having the same mutation, there

was a heterogeneity in the clinical and biochemical presentation, which implies the critical impact of other factors such as environmental influence and epigenetics.

The diagnosis of MEN1 can be established if the patient exhibits one of these criteria (Table 2) (Thakker et al. 2012). It was the first criterion that enabled the identification of MEN1 in case 1, whereas the second leads us to the diagnosis in the other siblings. Inactivation of this tumor suppressor gene have various implications including endocrine and non-endocrine tumors.

PHP in MEN1 is typically the earliest clinical manifestation of this syndrome characterized by precocious age of onset when compared with sporadic PHP (sPHP) as well as mild hypercalcemia, mild increased PTH contrasting with pronounced hypophosphatemia, which is compatible with our findings except for Case 3. One of the hypotheses emitted to explain these findings is that PTH have an increased bioactivity in MEN1 (Eller-Vainicher et al. 2009). The risk of recurrent or persistent PHP is multiplied in this genetic condition attributable to multi-gland disease and/or ectopic gland (Thakker et al. 2012) in the same way as for Case 2.

Otherwise, the association of MEN1 and thyroid tumors is controversial and incidental to some (Thakker et al. 2012), and a corollary to the gene defect in another research (Xu et al. 2022). This discrepancy is probably related to the paucity of academic work channeled to study thoroughly this topic. In our group, all siblings had non-auto-immune multinodular goiter except Case 2. Stunningly, she had ectopic parathyroid gland in the thyroid gland, which is a very rare finding not only in the general population, but also in MEN1 patients (Liu et al. 2022).

Another astonishing feature of this family, is the presence of a PTC in one of the sisters (Case 4). Whether PTC is a component or not of MEN1 is yet to be determined. Some studies shed light on this question and proved the absence of loss of heterozygosity (LOH) in thyroid cancerous cells,

which suggests the absence of interrelation between these two conditions (Desai et al. 2001; Kim et al. 2008; Perakakis et al. 2016). This notion of LOH is based on the Knudson's theory involving a two-hit procedure leading to cancer. One inherited allele of the tumor suppressor gene is mutated (in our case, it's the *MEN1* gene) and the second allele undergoes structural alterations within the somatic cells (Desai et al. 2001). Therefore, LOH is an indication of the direct responsibility of the gene mutation in tumorigenesis. In this setting, substantial evidence is warranted.

Regarding the pituitary adenomas in MEN1, they are frequently macroadenomas appearing at a median age of 38 ± 15 years, invasive, inclined to be resistant to therapy dominated as sporadic cases by prolactinomas. Likewise, our patient (Case 1) at an age of 31 years had a diagnosis of macroprolactinoma and was unresponsive to therapy.

Adrenal tumors are frequently encountered in the setting of MEN1 present in 20 to 73% of cases mostly non-functioning. Primary hyperaldosteronism and adrenocorticotrophic hormone (ACTH)-independent Cushing syndrome are the most prevailing among the functioning tumors. The risk of developing an adrenal carcinoma is exceedingly high in MEN 1 patients, hence the need for annual CT. The surgery is indicated if the mass exhibits atypical radiological features (Thakker et al. 2012).

Albeit DPNETs is a typical facet of this disease, none of our patients showed clinical nor radiological signs in favor of these tumors. Along with endocrine tumors, a constellation of non-endocrine tumors is associated with MEN1: lipomas (30%), leiomyomas, tumors of central nervous system, and collagenomas (Mele et al. 2020).

Concerning the underlying genetic defect in our study population, they all displayed a nonsense mutation of the 4th exon of the *MEN1* gene, which is a rather common finding in MEN1 (17% of the mutations are nonsense). As demonstrated above in our case studies and despite all siblings having

Table 2
Diagnostic criteria of MEN1 syndrome

1	The association of two endocrine tumors common in MEN1 (PHP, PA and NETs)
2	An individual with MEN1 associated tumor and a first degree relative with confirmed MEN1
3	A patient with MEN1 mutation

Abbreviations: MEN1 - multiple endocrine neoplasia type 1, NETs - neuroendocrine tumors; PA - pituitary adenomas; PHP - primary hyperparathyroidism.

the same mutation, there was a heterogeneity in the clinical and biochemical presentation, which implies the critical impact of other factors such as environmental influence and epigenetics. This lack of phenotype/genotype correlation has been highlighted by another research (Kim et al. 2008; Mele et al. 2020). However, data are still scarce regarding this subject.

Finally, the long-term follow-up is a major pillar of the management of MEN1 since early detection of tumors, especially neuroendocrine ones, which are distinctive in the context of MEN1 by their aggressive behavior and represent a major cause of death (Al-Salameh et al. 2021). Guidelines stipulate the necessity of annual biochemical assessment involving (calcemia, PTH, fasting glucose, insulin, chromogranin A, VIP, glucagon, pancreatic polypeptide, prolactin and IGF1) frequent imaging studies: annual thoracoabdominal CT aiming to screen for thymic or bronchial carcinoid, DPNET and adrenal tumors, and pituitary MRI every three years (Thakker et al. 2012).

Conclusion

MEN1 is a rare disease ascribed to a genetic defect within the *MEN1* gene predisposing affected individuals to a wide array of debilitating conditions with enormous impact on their quality of life. It seems that the genotype is not a sole factor altering the phenotype and other elements may be implicated as demonstrated by our case series. The management of MEN1 is quite burdensome since surgery can be required and long-term follow-up is crucial.

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