

lar enlargement, and no other signs of sexual development; some mechanisms proposed for this phenomenon implicate the NROB1 gene in the prepubertal control mechanism of the gonadal axis, ACTH-mediated stimulus of testicular steroidogenesis, or autonomous hyperplasia of Leydig cells.<sup>2</sup> In the pubertal period, these patients will require testosterone replacement for the development of secondary sexual characteristics. Since *DAX1* abnormalities may affect testicular development and spermatogenesis, fertility treatment using pulsatile GnRH and gonadotropins is often ineffective.<sup>4</sup> Mental disability (motor, speech, and social behavior) may also occur. To our knowledge, there are no cases reported in the literature of an association between *DAX1* and GH deficiency as seen in case 1.

*DAX1* mutations account for 58% of cases of primary adrenal insufficiency of "unknown etiology" in children (newborn-13 years) in whom autoimmune causes, deficient steroidogenesis, or metabolic causes have been ruled out.<sup>5</sup> Although it does not change the therapeutic strategy, molecular diagnosis allows for genetic counseling to relatives and is warranted in children with the onset of a salt-losing syndrome of unknown etiology, with or without associated cortisol deficiency. High clinical suspicion is required to prevent erroneous diagnosis and to allow for an adequate therapeutic approach.

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## Thymic carcinoid in the setting of a multiple endocrine neoplasia syndrome (MEN 1). Prophylactic thymectomy?<sup>☆</sup>

### Carcinoide tímico en el contexto de un síndrome de neoplasia endocrina múltiple (MEN 1). ¿Timectomía profiláctica?

The thymus gland is one of the most common sites of neuroendocrine tumors. Approximately 150 cases have been reported since 1972, of which 25% were associated with multiple endocrine neoplasia type 1 syndrome (MEN 1).<sup>1</sup> Thymic carcinoid has been reported in 2.6-5% of patients with MEN 1 in retrospective series.<sup>2</sup>

This type of tumor is more frequent in males, mostly smokers (>95%), and is usually non-functioning. It is the most common cause of anterior mediastinal masses in patients with MEN 1. The tumor is generally detected in advanced stages based on local symptoms or as a chance radiographic finding, and shows an aggressive behavior in most cases.

The most common cause of death in current MEN 1 is potential malignancy of gastroenteropancreatic neuroendocrine tumors,<sup>3</sup> which are more frequent than thymic carcinoids. However, since the effectiveness of the treatment of these tumors has increased, some studies have suggested that it is the development of thymic or other carcinoids that limits survival in patients diagnosed with MEN 1. This is because they are much more aggressive, depending on their histology and local invasion.<sup>1,2,4</sup>

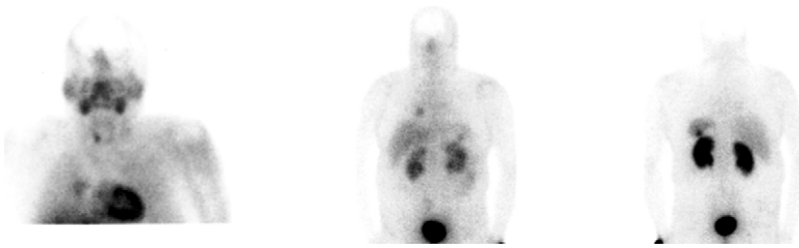
The natural history, results of early diagnosis, survival, or most adequate treatment are still unknown.

We report the case of a 48-year-old male patient who underwent surgery through a trans-sphenoidal approach for pituitary macroprolactinoma at 25 years of age, and repeat surgery four years later through a left frontoparietal craniotomy followed by residual tumor radiotherapy. At 32 years of age, after suffering a perforated ulcer, he was diagnosed with multicentric pancreatic gastrinoma, and treatment was started with proton pump inhibitors and somatostatin analogs.

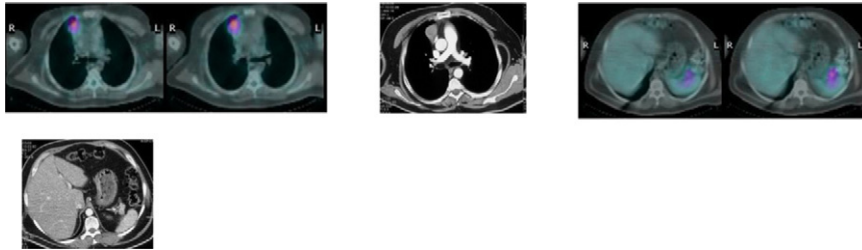
Primary hyperparathyroidism secondary to parathyroid hyperplasia was not detected until the age of 37. This is unusual, because this is usually the first sign in patients with MEN 1. Total parathyroidectomy was performed.

A genetic study in that same year revealed the presence of the Q450X familial mutation in exon 9 of the MEN

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**Figure 1** Somatostatin receptor scintigraphy. Planar images of the head, chest, and abdomen at 4 and 24 h. Planar images show two nodular lesions with a high density of somatostatin receptors in the right hemithorax and in front of the inferior plane of the spleen.



**Figure 2** SPECT-CT of the chest and abdomen allows for the localization of both lesions: the thoracic lesion in the anterior mediastinum and the abdominal lesion in the tail of the pancreas (an already known gastrinoma with no significant changes from prior images).

1 gene. A subsequent extension of this study to all first-degree relatives found the same mutation in his father and brother.

At the age of 38 years, a control octreotide scan showed two nodular lesions with an increased uptake of somatostatin receptors. One of the lesions was the already known gastrinoma, while the other was located in the anterior mediastinum (Figs. 1 and 2). Total thymectomy through a median sternotomy was performed. The pathological report confirmed the diagnosis of a 5-cm thymic carcinoid invading the capsule. Radiotherapy was subsequently administered. Six months after surgery, tumor recurrence had not been seen in either scintigraphy or CT.

The unique characteristic of the reported case was the diagnosis of a pituitary adenoma as the first indication of MEN 1. In fact, primary hyperparathyroidism is the most common presentation, with a 100% penetrance. A literature review discussing the most widely accepted recommendations for managing patients with MEN 1 is provided below.

The 2001 consensus guidelines for the diagnosis and treatment of MEN 1 and MEN 2<sup>5</sup> state that thymic carcinoid is more common in MEN 1, particularly in males, while bronchial carcinoid occurs more frequently in females. Thymic carcinoid is more aggressive in MEN 1 than in sporadic cases, and CT or MRI is recommended for early diagnosis, but no specific time intervals for follow-up are given. Near-total thymectomy concomitant with parathyroidectomy is recommended.

A prospective study of 85 patients with MEN 1<sup>1</sup> followed up for a mean of 8 years with CT, MRI, chest X-rays, and, since 1994, with octreoscan was published in

2003. Seven of these patients (8%) developed a thymic carcinoma. Carcinoid was diagnosed in four patients based on routine morphological assessment and in two patients based on clinical symptoms of cough and chest pain. In the remaining patient, carcinoid was an incidental finding at repeat parathyroid surgery. All patients were male (mean age, 55 years), and 86% also had Zollinger–Ellison syndrome. In no patient was thymic carcinoid the first sign of MEN 1. All patients were hormonally inactive. Tumor presence was confirmed in 100% of patients by CT or MRI, in 75% using somatostatin receptor scintigraphy, and in 66% by chest X-rays. Bone metastases occurred in two patients (28%) diagnosed by MRI but not by scintigraphy. Radiographic recurrence of the disease was found in all patients at one-year follow-up after surgery.

A study of patients with MEN 1 from the Italian register was published in 2005.<sup>4</sup> Seven cases of thymic carcinoid were diagnosed in a series of 221 patients with MEN 1, 41 sporadic and 180 familial, i.e. a 3.1% prevalence. They all were male patients, with a mean age at presentation of  $38.7 \pm 9.9$  years. Eighty-five percent of them were smokers. Six patients were asymptomatic at diagnosis, which was made based on a mediastinal mass incidentally found in an imaging test. No hormone secretion or carcinoid syndrome was detected in any case, and urinary hydroxyindoleacetic acid levels were normal in all patients. A slight increase was detected in serum enolase and chromogranin A levels. During follow-up, three patients died from diffuse metastases 60, 36, and 26 months after surgery. One patient had locoregional metastases 96 months after surgery but, at the time of writing, is stable, while two patients show no evidence of disease after 28 and 120 months, respectively, and one patient undergoing prophylactic thymectomy with a sub-

sequent pathological report of carcinoid is free of disease 84 months later.

In 2009,<sup>2</sup> a group of 761 patients with MEN 1 registered by the *Groupe des tumeurs Endocrines* (GTE) was analyzed, and 21 patients were diagnosed with neuroendocrine thymic tumors (2.8%). All patients but one were male, and mean age at diagnosis was 42.7 years. The youngest patient in the series was 16 years old. Mean approximate survival was 9 years and 7 months, with a 70% mortality, which confirms the poor prognosis of thymic carcinoid tumors in the setting of MEN 1. There was no specific or sensitive marker for tumor detection, and no specific associated genetic mutation. Both MRI and CT were consistently positive for diagnosis. Among the 21 patients analyzed, 11 had prior hyperparathyroidism and 6 developed thymic carcinoid tumors after prophylactic thymectomy through a median cervicotomy, which may suggest the relative difficulty of total thymus removal using such an approach.

Based on the foregoing, we conclude that it is advisable to make an early diagnosis of thymic carcinoid in patients of both sexes with MEN 1 by annual CT or MRI, and to perform total thymectomy in all patients during the same surgical procedure as parathyroidectomy at specialized centers. These recommendations are based on the invasive potential of these tumors, the lack of predictors, and the low morbidity of the procedure despite the uncommon occurrence of this type of tumor. However, this measure does not completely prevent the development of thymic carcinoid, and since we cannot predict which patients will develop it, they should all be monitored.

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## Seizure in a diabetic patient. Hypoglycemia or a side effect of continuous glucose monitoring?☆

### Crisis comicial en paciente diabética. ¿Hipoglucemia o efecto secundario de la monitorización continua de glucosa?

Optimization of treatment of diabetes mellitus involves an increased risk of hypoglycemia,<sup>1–3</sup> which may be asymptomatic.<sup>4</sup> On the other hand, seizures may be triggered by hypoglycemia,<sup>5,6</sup> and the monitoring of patients with both diabetes and epilepsy therefore requires special attention.

We report a female patient with type 1 diabetes mellitus (T1DM) and epilepsy with generalized tonic-clonic and complex partial seizures and photosensitive absences who experienced a seizure while carrying a continuous glucose monitoring (CGM) device. The patient was 35 years old at the time of the episode and had been diagnosed

with T1DM at 7 years and with epilepsy at 16 years. Her seizures were usually triggered by stress, sleep deprivation, and hypoglycemia. The patient's DM had been treated with an insulin pump since 2003, before her pregnancy. This treatment had been discontinued after delivery and restarted in 2006 due to poor glycemic control treated with multiple doses of insulin analogues. Glycosylated hemoglobin (HbA<sub>1c</sub>) level was 7.2% in the months preceding admission, but since the patient was being monitored for pregnancy, intermittent CGM was decided upon to improve glycemic control. The patient had been treated for epilepsy since 2002 with lamotrigine (current dose, 500 mg/day) and experienced 1–2 seizures per year, most of them coinciding with one of the abovementioned triggering factors.

In July 2010, she was brought by ambulance to the casualty ward of the hospital after suffering a tonic-clonic seizure at midday in her workplace. Blood glucose on arrival was 147 mg/dL. The patient showed bradypsychia, but no focal neurological signs or other abnormalities on examination. She had had a continuous glucose infusion pump implanted and a glucosensor inserted 2 days before. Thirty minutes after arrival, the patient experienced two episodes of the same characteristics that were treated with clonazepam. The concomitant blood glucose level was 140 mg/dL. Impregnation was started with valproic acid,

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