

patients with a multinodular thyroid gland, autonomous nodules, or latent Graves-Basedow disease due to increased thyroid hormone production and release.<sup>2</sup> Its incidence is 1.7%.

Areas with adequate iodine intake have a low incidence of hyperthyroidism induced by excess iodine intake.

Euthyroid patients with some prior episode of postpartum thyroiditis, type 2 amiodarone-induced thyrotoxicosis, or interferon-induced thyroid dysfunction are more susceptible to develop hyperthyroidism due to excess iodine intake (up to 20%), as are patients with multinodular thyroid, autonomous nodules, or diffuse goiter.<sup>3,4</sup> In the latter, the prevalence ranges from 3.5% to 21% depending on iodine exposure.

Iodine intake may set the course in patients with Graves-Basedow disease, because a slight increase in dietary iodine results in a greater frequency of hyperthyroidism and a decreased efficacy of antithyroid treatment.<sup>5</sup> In addition, in iodine-deficient areas, the response to antithyroid agents is better and lower doses are required for hormone control.<sup>6</sup>

It is therefore essential to consider the potential factors leading to excess iodine intake when faced with difficult to control Graves-Basedow disease (Table 2).

In the case of our patient, the course of hyperthyroidism led us to decide upon a definitive treatment. The clinical condition of the patient and the course of events prevented us from detecting excess iodine intake before surgery or a potential improvement after the removal of povidone iodine, but a more satisfactory response to drug treatment could have been expected in the absence of excess iodine intake.

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## Primary hyperparathyroidism and acute pancreatitis<sup>☆</sup>

### Hiperparatiroidismo primario y pancreatitis aguda

Sir,

Primary hyperparathyroidism (PHPT) is the leading cause of hypercalcemia in a hospital setting and has an incidence of 1–2 cases/1000 admissions. The biochemical and clinical manifestations of PHPT are related to increased PTH levels or hypercalcemia.<sup>1</sup> In addition, associated syndromes such as high blood pressure, peptic ulcer, chondrocalcinosis, or acute pancreatitis (AP), whose relationship to phosphate and calcium metabolism disorders have not been fully elucidated, may occur.<sup>1</sup>

We report a 26-year-old male patient with a history of allergy to erythromycin, a smoker of 20 cigarettes

daily who was diagnosed in February 2010 with AP of unknown etiology based on Ranson criteria. The etiological study was performed on an outpatient basis. Laboratory test results included: serum calcium 11.3 mg/dL, corrected calcium 10.5 mg/dL, urinary calcium 29 mg/dL, phosphate 2.6 mg/dL, and PTH 333 pg/mL. PHPT was suspected, and imaging tests were requested to discover its location. MRI and scintigraphy with Tc-99 showed images consistent with a right upper parathyroid adenoma. No personal or family history of tumors related to multiple endocrine neoplasia syndrome was found. In February 2011, right upper parathyroidectomy was performed with selective access. The baseline intraoperative PTH level was 376 pg/mL, but its value decreased to 26 pg/mL after resection. The pathological report confirmed the diagnosis of parathyroid adenoma. In the early postoperative period, the patient experienced severe abdominal pain associated with nausea, vomiting, and abdominal distention. Laboratory tests showed at that time an amylase level of 500 IU/L and a calcium level of 8.2 mg/dL. The abdominal ultrasound performed showed no changes. AP was diagnosed based on clinical signs and symptoms, and showed a successful course with conservative treatment. At subsequent visits, the patient

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remained asymptomatic, with normal calcium and PTH levels.

Hypercalcemia secondary to PHPT is an uncommon cause of AP. Although the association was initially reported in 1947, it was not fully accepted until 10 years later. Today, the relationship between AP and PHPT is well recognized. Patients with PHPT and hypercalcemia have a 10-fold greater risk of suffering AP as compared to the general population.<sup>2</sup> Pancreatic disease is however an uncommon complication (occurring in approximately 2% of patients with PHPT).<sup>2</sup> However, the pathophysiological mechanism that relates them has not been fully elucidated. Moreover, few references can be found in the medical literature, which has not promoted its clinical or epidemiological understanding. AP most commonly occurs in the setting of a documented PHPT.<sup>2</sup> The reported case is particularly interesting. On the one hand, it is uncommon to find a young patient in whom AP leads to a diagnosis of PHPT, and on the other hand, the occurrence of two sequential episodes of AP, one of them after parathyroidectomy, is also noteworthy. The conclusion to be drawn is that hypercalcemia occurring in the setting of AP may be the first sign of PHPT.<sup>3</sup>

Although no clear pathophysiological basis has been established, it seems that the association of AP and PHPT is not a chance association and that calcium levels are the main causative factor. Thus, a direct relationship appears to exist between calcium levels and pancreatitis severity.<sup>2</sup> Several hypotheses have been proposed to try and explain the relationship between PHPT and AP. Thus, Kelly et al.<sup>4</sup> showed, using an experimental model, that high calcium levels increase calcium concentrations in pancreatic juice, which promotes the conversion of trypsinogen into active trypsin. More recently, Ca<sup>2+</sup> elevation in cytosol has been shown to trigger PA.<sup>5</sup> Hypercalcemia could promote the activation of pancreatic enzymes through lysosomal acid hydrolases.<sup>2</sup> In recent years, attention has been paid to the existence of a genetic substrate. Mutations in the SPINK1 (serine protease inhibitor Kazal type I) and CFTR (cystic fibrosis transmembrane conductance regulator) genes have been detected in patients with PHPT who developed AP.<sup>6</sup> Mutations have also been found in the CTSC (chymotrypsin C) gene.<sup>7</sup> SPINK1 is a specific trypsin gene, the mutated variant of which has a decreased capacity to inhibit trypsin, which may be prematurely activated in the pancreas.<sup>6</sup> There are also variants of the anionic trypsinogen gene PRSS2 which appear to exert some protective effect against the occurrence of AP in patients with PHPT.<sup>8</sup> The CASR (calcium-sensing receptor) gene has also been implicated,

but its role in this process is not clear.<sup>2</sup> These genes are involved in the regulation of lysosomal membrane permeability, in intracellular calcium homeostasis, and in trypsin activation control. Thus, hypercalcemia alone does not cause AP, but mutations in the abovementioned genes promote the development of AP.

In conclusion, hypercalcemia causes AP in patients with PHPT. High calcium levels in a patient with AP may be the first manifestation of PHPT. The pathogenesis of this condition is not well known, but appears to have a genetic basis.

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