Pituitary mass induced by pharmacological interaction

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ABSTRACT

يعتبر بروز كتلة الغدة الدرقية النخامية كحدث ثانوي ناتج عن تفاعل الدواء إثر قصور الغدة الدرقية أمر نادر الحدوث. إن إهمال الربط بين مكونات المرضية يمكن أن يؤدي إلى علاج جراحي في الوقت الذي يمكن الاكتفاء بالعلاج الطبي مع تحقيق نتائج باهرة. يهدف هذا المقال إلى توضيح أهمية اليقظة الدوائية في حالات قصور الغدة الدرقية الناجم عن التفاعلات الدوائية. نستعرض في هذا التقرير حالة مريضة تبلغ من العمر 41 عام تعاني من بروز كتلة الغدة الدرقية النخامية كحدث ثانوي ناتج عن تفاعل الدواء إثر قصور الغدة الدرقية. تم إنقاص جرعة الثيروكسين والكالسيوم واستخدم علاج جديد لفترة 3 ساعات بين إعطاء الثيروكسين والكالسيوم. تحتوي النتائج على تطور ملحوظ للأعراض البوثولجية والطبية والحيوية والأعراض.

A pituitary mass secondary to peripheral hypothyroidism drug interaction is rare. Very few cases are reported in the literature. Neglecting this pathological association that is not initially obvious, might lead to very invasive surgical treatment, while the pathology could have a very good outcome using medical treatment. The goal of this paper is to illustrate the importance of pharmacovigilance in patients suspected with hypothyroidism induced by drug interaction. We report a 41-year-old women presenting a pituitary mass secondary to hypothyroidism originated from L-thyroxine malabsorption induced by interaction with calcium. The patient underwent dose reduction of L-thyroxine and calcium, and the new therapy protocol included a 3 hour interval between L-thyroxine and calcium administration. The results consisted of important regression of the clinical, biological, and imaging symptoms.

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Secondary pituitary hyperplasia in primary hypothyroidism might demonstrate a pseudo tumoral aspect, which responds well to a substitutive organotherapy protocol of treatment. The pathology is a consequence of a failed thyroxin negative feedback mechanism, this yields an increase in thyroid-stimulating hormone (TSH) secretion leading in turn to pituitary hyperplasia. Pituitary adenoma remains the most frequent lesion in human adults. The imaging techniques, especially MRI, have better demonstrated these secondary pituitary masses, allowing the avoidance of invasive surgical therapy.[1-3] We report a case of a woman presenting a secondary pituitary tumoral syndrome in peripheral hypothyroidism induced by drug interaction. Our objective in presenting this particular case is to illustrate the importance of studying drug interactions in patients taking more than one medication. We also discuss the role of pharmacovigilance.

Case Report. A 41-year-old woman presented with temporo-frontal headaches of sudden appearance and spanemia. Her history consisted of previous surgery for multi-nodular goiter, and a total thyroidectomy was carried out and was complicated with hypoparathyroidism. She underwent substitutive organotherapy consisting of 200 µg/day thyroxin, 2 g/day calcium, and 2 µg/day vitamin D (Alfa calcidiol). Regular follow-up showed normal TSH values and calcemia. The symptoms evolved over 3 months. She presented temporal-frontal headaches, and permanent pulsation without improvement with the usual analgesic treatments. Cycle disorders of the spanemia type also occurred. These symptoms were associated with a higher TSH rate, despite good therapeutic performance. Clinical examination revealed discreet signs of hypothyroidism without any associated signs, especially clinical signs of hypocalcemia, pre-pituitary dysfunction, and galactorrhea. The biological

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assessment confirmed hypothyroidism with a TSH rate higher than 100 µUI/ml (normal range 0.3-3.00 µUI/ml), moderate hyperprolactinemia of 30.21 ng/ml, oestradiol of 31 pg/ml, basic cortisolemia of 9.29 µg/dl. The Synacthen test for the adrenal gland indicated cortisolemia with a value of 277 µg/dl, which is higher than the reference value of 21 µg/dl. The blood formula assessment demonstrated normochromic anemia. Lipid assessment showed high cholesterol levels of 3.50 g/l, with a corrected calcemia of 94 mg/l. Her clinical profile and TSH results suggested thyroid hormone malabsorption. This was confirmed by LT4 assessment, 2 hours after drug intake the LT4 decreased to 1.15 pg/ml (normal values 5.8-16.4 pg/ml). Therefore, the diagnosis of thyroid hormone resistance syndrome was eliminated. In consideration of pituitary tumoral syndrome, a hypothalamic-pituitary MRI was carried out, and the results revealed a pseudo pituitary tumor with pituitary hyperplasia of the pituitary stem and chiasma opticum (**Figure 1**). An ophthalmic examination showed full alteration of visual fields, with normal fondus. Therapeutic ineffectiveness was suggested considering the higher TSH levels despite 200 µg of L-thyroxine. Therefore, a possible drug interaction involving L-thyroxine and calcium was suspected. The interaction between the calcium and L-thyroxine study was carried out in the Pharmacology and Pharmacovigilance department. Decreased thyroxin absorption was recorded when both L-thyroxine and calcium were administered simultaneously. The final diagnosis was a secondary pituitary mass following treatment for primary hypothyroidism induced by drug interaction between thyroxin and calcium. Treatment consisted of a reduction in the calcium dose to one g/day and L-thyroxine to 100 µg/day; a delay of 3 hours between administration of each drug was observed. An improvement in clinical symptoms and regression of headaches were noticed one week after introduction of the new treatment protocol and spacing of drug administration.

An evaluation after one week was marked by the disappearance of headaches and hypothyroid signs. Two months later, the amenorrhea disorder had disappeared, and the LT4 rates normalized at 1.44 ng/dl on 100 µg/day of L-thyroxine (normal range: 0.89-1.76 ng/dl). The hypothalamo-pituitary MRI demonstrated a normal size pituitary gland without pituitary stem abnormality (**Figure 2**). The visual field was normal, this allowed confirmation of the vision reaction character such as a peripheral component of hypothyroidism. The TSH rate required 3 months to normalize at 4.2µUI/ml (normal range 0.34-5.60 µUI/ml).

Discussion. Secondary pituitary hyperplasia in primary hypothyroidism was identified in the 19th century.[1] The incidence of pituitary gland volume increase was noticed during the peripheral hypothyroidism and varies from 25-81%. Khawaja et al[2] reported an incidence of up to 70% in patients with a TSH >50mUI/ml. Pituitary hyperplasia is a physiological reaction occurring at birth, puberty, during pregnancy and in the post-partum period. The anatomicopathological findings demonstrate

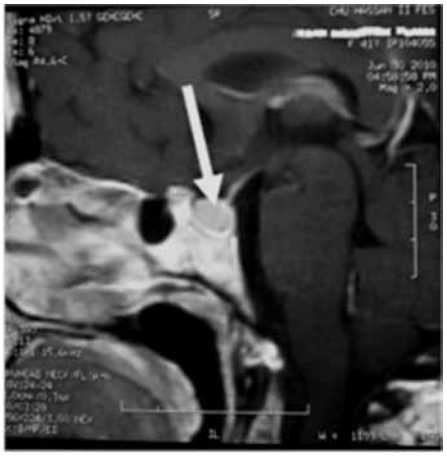

Figure 1 - The T1-weighted MRI demonstrating a pituitary hyperplasia (arrow).

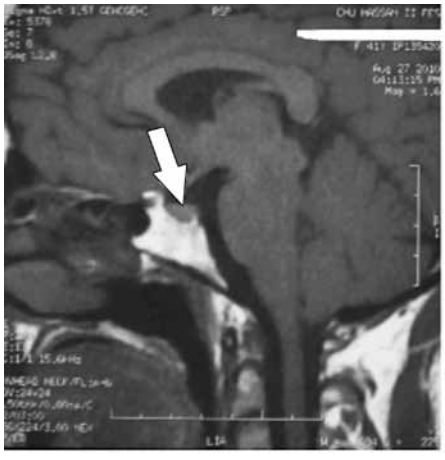

Figure 2 - The T1-weighted MRI of control after 2 months of treatment demonstrating a complete normalization of previous pituitary hyperplasia.

hyperplasia of thyreotrope and/or lactotrope cells.[3] The pathophysiological mechanism argument explained the pituitary hyperplasia, which involved failed hypothyroid feedback. Indeed, increased hypothalamic thyrotropin-releasing hormone (TRH) secretion in peripheral hypothyroidism stimulates TSH and prolactin. This TRH is slowed down by dopaminergic secretion of hypothalamic origin. The first hypothesis consisted of a reduction of dopaminergic, hypothalamic, and suppressive activities. However, the increase of TRH in hypothyroidism was contested; hence the hypothesis of a sensitivity of lactotropin cells to the TRH we evoked.

Hyperplasia of the pituitary gland in primary hypothyroidism is often asymptomatic. However, symptoms of a pituitary mass are expressed such as chiasmatic compression, galactorrhea, headache, amenorrhea, and so forth. Despite recent progress in imaging methods, it is still difficult to differentiate pituitary adenoma and pituitary hyperplasia. The MRI evaluation of amenorrhea, galactorrhea, hyperprolactinemia, and inappropriate secretion of TSH, might increase detection of pituitary hyperplasia, therefore leading to differentiate between pituitary adenoma and a hyperplasia. Various MRI signs allow differentiating between hyperplasia and pituitary adenoma. However, the most suggestive sign is the projection of the median line of the pituitary mass with the smooth edge known as "nipple sign". However, the diagnosis has to be based on the patient history, especially the initial TSH level, coexistence of disorders or of over-the-counter (OTC) medications,[4] which could interfere with the absorption of the thyroid hormones, and the engagement level of the patient to the treatment.[5]

This case demonstrated hypothyroidism secondary to thyroxin malabsorption induced by drug interaction with calcium; this interaction was the origin of the decrease in thyroxin absorption. Four case reports have previously confirmed the significance of this interaction.[5,6] The absorption of thyroid hormones is mainly achieved via the duodenum and the ileojejunum. This absorption is incomplete and variable. Various physiological, pathophysiological factors, and drugs can impact this absorption (**Table 1**).[4,7,8] The normalization of the thyroid assessment, and the size of the pituitary gland following 2 months of treatment by 100 µg/day thyroxin and 1g/day calcium, respecting a 3 hour interval between the intake of thyroxin and calcium confirms the diagnosis of a secondary pituitary mass in the peripheral hypothyroidism, itself secondary to the drug interaction between thyroxin and calcium. The response time required for the regression of the pituitary hyperplasia by L-thyroxine treatment is not well defined. It has been reported that a pituitary mass regressed within 40 days of treatment, or spectacularly after only 6 days. The evolution of pituitary hyperplasia treated by thyroid hormones must be closely managed since it might potentially demonstrate rare acute neurological symptoms, visual deficit, and a pituitary adenoma, which does not decline in response to substitutive therapy with thyroxin. In our reported case, we obtained normalization of the hypothalamic-pituitary MRI results and normal examination of the eyes fondus and visual fields following 2 months of treatment (**Figure 1b**).

In conclusion, this reported case underlines the importance of investigating drug interaction in primary hypothyroidism in patients receiving multiple medication doses. Pharmacovigilance allows the basic study of all the hypothalamic-pituitary axis during pituitary hyperplasia. The interpretation of a pituitary mass without an endocrine investigation and without a pharmacovigilance study might lead to a useless and very invasive surgery with irreversible complications.

Table 1 - Drug samples interacting with thyroid hormones and mechanisms of interaction.

Drugs	Interaction mechanisms with thyroid hormones
Iron salt, colestyramin, calcium components	Decreased absorption
Propranolol, amiodarone	Inhibition of iodine elimination
Sertraline	Increase of the clearance
Lovastatin, simvastatin, anti-convulsants, imatinib	Increased hormonal catabolism by enzymatic induction of cytochrome P450 1A2 (abbreviated CYP1A2) and/or cytochrome P450 3A4 (abbreviated CYP3A4)

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CASE REPORTS

Case reports will only be considered for unusual topics that add something new to the literature. All Case Reports should include at least one figure. Written informed consent for publication must accompany any photograph in which the subject can be identified. Figures should be submitted with a 300 dpi resolution when submitting electronically or printed on high-contrast glossy paper when submitting print copies. The abstract should be unstructured, and the introductory section should always include the objective and reason why the author is presenting this particular case. References should be up to date, preferably not exceeding 15.