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Original article

High prevalence of autoimmune thyroid diseases in patients with prolactinomas: A cross-sectional retrospective study in a single tertiary referral centre

Forte prévalence des maladies autoimmunes de la thyroïde chez les patients atteints de prolactinome : étude transversale rétrospective monocentrique dans un centre de référence tertiaire

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Abstract

Background. – Prolactin has been shown to exert potent immunomodulatory activities. *Design.* – Retrospective cross-sectional study examining the prevalence of autoimmune thyroid diseases (AITD) in patients with prolactinomas. The medical files of 462 patients (367 women and 95 men) followed up at a single tertiary referral centre were analyzed. *Results.* – The prevalence of AITD among prolactinoma patients was estimated at 21.0% (23.2% in females and 12.6% in males). In 51.5% of the patients, diagnosis of prolactinoma preceded the development of AITD; in 37.2%, both diseases were simultaneously diagnosed and 11.3% of patients were diagnosed first with AITD. Hyperthyroidism was observed in 1.24% of the investigated subjects. Primary hypothyroidism was detected in 15.6% of all patients (16.4% in women; 10.7% in men) with a mean incidence of 24 cases/1000/year. *Conclusions.* – Our results demonstrate the high frequency of AITD in patients with prolactinomas. The prevalence rate of hyperthyroidism is comparable with the literature data from community-based studies. In contrast, the prevalence of the spontaneous hypothyroidism due to autoimmune thyroiditis is significantly higher in female and male subgroups of patients with prolactinomas in comparison with the general population. A possible role of supraphysiologically increased prolactin levels in the pathogenesis and the clinical course of AITD in patients with prolactinomas can be suggested. Based on these findings we recommend routine screening for AITD with simple thyroid tests (TSH, TPO-Abs and ultrasound examination) in all patients diagnosed with prolactinoma.

Keywords: Autoimmunity; Prolactin; Thyroid diseases; Hyperprolactinemia; Prolactinoma

Résumé

Introduction. – Une puissante activité immunomodulatrice a été démontrée pour la prolactine. *Méthodes.* – Étude rétrospective transversale étudiant la prévalence des maladies autoimmunes de la thyroïde (AITD) chez les patients atteints de prolactinome. Les dossiers médicaux de 462 patients (367 femmes et 95 hommes) suivis dans le centre de référence tertiaire ont été analysés. *Résultats.* – La prévalence des AITD chez les patients atteints de prolactinome a été estimée à 21,0 % (23,2 % chez les femmes et 12,6 % chez les hommes). Chez 51,5 % des patients le diagnostic de prolactinome précédait le développement des AITD ; chez 37,1 % d'entre eux, les deux maladies ont été diagnostiquées simultanément tandis que 11,3 % des patients avaient en premier lieu un diagnostic d'AITD. Une hyperthyroïdie a été observée chez 1,24 % des sujets étudiés. Une hypothyroïdie primaire a été retrouvée chez 15,6 % de l'ensemble des patients (16,4 % chez les femmes ; 10,7 % chez les hommes) avec une incidence moyenne de 24 cas/1000/année. *Conclusions.* – Nos résultats démontrent la fréquence élevée des AITD chez les patients souffrant de prolactinome. Le taux de prévalence de l'hyperthyroïdie est comparable avec les données de la littérature à partir d'études communautaires. En revanche, la prévalence de l'hypothyroïdie spontanée due à une thyroïdite autoimmune est significativement plus élevée dans les sous-groupes

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femelle et mâle de patients atteints de prolactinome par rapport à la population générale. Une augmentation supraphysiologique des taux de prolactine dans la pathogenèse et l'évolution clinique des AITD chez les patients atteints de prolactinome peut être suggérée. En nous fondant sur ces résultats, nous recommandons le dépistage systématique des AITD avec des tests simples de la thyroïde (TSH, TPO-ABS et échographie) chez tous les patients avec un diagnostic de prolactinome.

Mots clés : Autoimmunité ; Prolactine ; Maladies thyroïdiennes ; Hyperprolactinémie ; Prolactinome

1. Introduction

Over the past two decades considerable evidence has been accumulated indicating that prolactin can act as a potent immunomodulator. This hormone has been shown to influence both humoral and cell-mediated responses through binding to its specific receptors which are expressed on monocytes, macrophages, T- and B-lymphocytes, natural killer cells (NK), granulocytes and thymic epithelial cells [1–3]. Experimental studies have demonstrated that prolactin enhances lymphocytes proliferation, activates T-lymphocytes via positive regulation of interleukin-2 (IL-2) and interferon regulatory factor-1 (IRF-1) genes and increases IFN-γ production from NK cells and T lymphocytes [4–6]. Hyperprolactinemia ameliorates the synthesis of IL-4 and IL-6 that are crucial for the B lymphocytes clonal expansion, growth, differentiation and maturation [7,8]. In accordance with these data hyperprolactinemia has been observed in many multi-organ and organ-specific autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjogren's syndrome (SS), Hashimoto's thyroiditis (HT) and celiac diseases [9–13]. Furthermore, a significant correlation has been reported between the PRL levels and the clinical disease activity of SLE and celiac disease [14–16]. On the other hand, only two small studies have been published investigating the prevalence of thyroid dysfunction and autoimmunity among patients with hyperprolactinemia compared to sex- and age-matched control subjects [17,18].

2. Patients and methods

2.1. Objective

The aim of this study was to determine the prevalence of autoimmune thyroid diseases (AITD) in an unselected population of patients with prolactinomas.

2.2. Study design

A retrospective cross-sectional study was conducted at a single tertiary referral centre. Two main data sources were used: the electronic medical records (Omni Pro Hospital Information System) and the paper patients' files (Hospital Archives).

2.3. Inclusion criteria

Subjects ≥ 18 years old with diagnosis prolactinoma based on current guidelines [19,20].

2.4. Exclusion criteria

The exclusion criteria were:

- hyperprolactinemia of non tumoral origin;
- negative pituitary imaging (CT, MRI);
- patients having had a single visit to the hospital;
- subjects coded as dead before cohort enrolment.

2.5. Additional exclusion criteria concerning the analysis of thyroid function

The additional exclusion criteria concerning the analysis of thyroid function were:

- hypopituitarism (in spite of the severity and the number of anterior pituitary hormone deficits; except the isolated transient hyperprolactinemic hypogonadotropic hypogonadism);
- past history of thyroid surgery;
- radiation of the neck region;
- previous or concomitant use of drugs with possible impact on thyroid function (iodine, lithium, etc.).

The diagnosis AITD was based on the presence of at least two of the following criteria: abnormal thyroid ultrasound pattern–diffuse non homogenous hypoechogenic structure with or without nodular changes; positive anti-thyroid peroxidase (TPO-Ab), anti-thyroglobulin (TG-Ab) and/or anti-TSH-receptor antibodies (TRAb); abnormal thyroid function estimated on data for serum concentrations of thyroid stimulating hormone (TSH), free thyroxine (FT4), and free triiodothyronine (FT3). Subclinical hyperthyroidism was defined as a low or undetectable serum TSH with values within the normal reference range for both FT4 and FT3 [21]. The presence of suppressed TSH levels in a combination with elevated FT4 and FT3 levels is considered overt hyperthyroidism. Subclinical hypothyroidism was defined as an increased TSH above the upper normal limit with normal FT4 and FT3 values. Cases with elevated TSH levels and thyroid hormones value under the lower normal range were categorized as having an overt