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Thyroid autoimmune disorders in patients with acromegaly

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Abstract
Purpose Disorders of the hypothalamic-pituitary-thyroid axis are common in patients with acromegaly and thyroid enlargement is present in the majority of them. The exact prevalence of goiter in patients with acromegaly remains uncertain and the presence of thyroid autoimmunity has not been extensively evaluated so far.
Methods We retrospectively evaluated thyroid biochemical and morphological findings in 116 acromegalic patients who attended our hospital. Serum TSH, total thyroxine levels and anti-thyroid peroxidase (ATPO) antibodies were measured by standard ultrasensitive techniques in all the patients. Thyroid ultrasound was performed in 75 out of them. The antibody control group was composed by healthy Argentinean individuals who attended the blood bank of our hospital in whom ATPO antibodies were measured.
Results Twenty-nine out of the 116 acromegalic patients (25 %) showed elevated titers of thyroid antibodies (79 % were women and 21 % men). The control group had a 10 % prevalence of thyroid autoimmunity. The prevalence of goiter by ultrasound was 36 %, being more common in females (41 %) than in males (28 %). Thirty-five percent of patients who presented thyroid nodules and 44 % of patients with ultrasound diagnosed goiters had positive thyroid autoimmunity. There was no significant correlation between the presence of nodules and IGF-1 levels, duration of disease or age.
Conclusion We found a high prevalence of thyroid autoimmunity in our patients with acromegaly as compared to the normal population. Thyroid autoimmunity seems to be an additional mechanism for the development of thyroid disorders in acromegaly.

Keywords Acromegaly · Thyroid autoimmunity · Goiter · Thyroid nodules

Introduction

Acromegaly is a chronic debilitating disease resulting from excessive growth hormone (GH) secretion, in most cases due to a GH-producing pituitary adenoma. The effects of GH are mediated mainly by stimulating the production of insulin-like growth factor-1 (IGF-1). Disorders of the hypothalamic-pituitary-thyroid axis are common in patients with acromegaly and thyroid enlargement is present in the majority of them [1–3]. Over the past two decades, with the development of more sensitive imaging techniques, prevalence of goiter and thyroid nodules has significantly increased. The pathogenesis of those problems in the context of acromegaly has not been completely elucidated. Some authors have reported a positive correlation between thyroid volume and age, body weight, serum GH and IGF-1 levels, duration of the disease, insulin levels or iodine deficiency [3–5]. Besides, thyroid cells express the IGF-1 receptor and TSH–IGF-1 interaction has been shown to have a synergistic effect in thyroid cell growth [5].

So far, the presence of anti-thyroid antibodies in patients with acromegaly has been poorly investigated in the literature and variable figures of prevalence have been shown in the few series which addressed this issue [5–8].

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In this study we retrospectively investigated the prevalence of thyroid antibodies in acromegalic patients attending our institution. We also analyzed thyroid morphological and functional features in this population in order to further understand the interaction of acromegaly with thyroid disease.

Patients and methods

We retrospectively evaluated the thyroid biochemical and morphological findings in 116 acromegalic patients (78 females and 38 men) with a mean age of 43.8 years (range 18–77 years) The diagnosis of acromegaly was based on the evidence of typical clinical features of GH hypersecretion, GH concentrations greater than 1.0 ng/ml during glucose suppression test and serum IGF-1 levels over the normal age and sex-matched range. The median time of evolution of acromegaly was 5.7 years (range 1–19).

All patients had at least basal measurements of TSH by second generation assays, total thyroxine levels and antithyroid peroxidase antibodies (TPO-Ab) measured by standard ultra sensitive techniques. IGF-1 determinations were made using different radioimmunoassay and quimioluminiscencia techniques so values obtained are represented as the percentage of the upper limit of normality (ULN-IGF-1) by age. In 81 out of 116 patients a thyroid ultrasonography was performed. The volume of each thyroid lobe was calculated from the formula L × W × D × pi/6 where L is the longitudinal length, W the transverse diameter and D is the depth of the lobe. Total thyroid volume was the sum of the volumes of the two lobes [9, 10]. Goiter was defined when the thyroid volume was >13 ml in females and >18 ml in males, which correspond to upper normal limits [5]. Thyroid nodularity was determined by ultrasonography and a nodule was defined as a definite formation exceeding 5 mm in diameter [10].

The antibody control group was composed of healthy Argentinean individuals who attended the blood bank of our hospital, as reported by Niepomniszcze et al. [11].

Results

The main findings of this retrospective evaluation are represented in Table 1. Twenty-nine out of the 116 acromegalic patients (25 %) showed elevated titers of thyroid antibodies. Among all patients with positive autoimmunity 79.3 % were women, mean age 49 years (26–71) and 20.7 % were men, mean age 48 years (32–75). The prevalence of thyroid TPO-Ab in the control group was 10 %. There was a statistically significant difference between these two groups ($p = 0.0032$; CI 17.3–53.9).

Table 1 Frequency of goiter and thyroid nodularity by ultrasound, positive thyroid autoimmunity, hypothyroidism and hyperthyroidism in 116 patients with acromegaly

Thyroid alteration	Acromegalic patients
Goiter (ultrasound)	36.0 % (27/75)
Nodularity (ultrasound)	45.7 % (37/81)
Positive autoimmunity	25.0 % (29/116)
Hypothyroidism	12.3 % (14/114)
Hyperthyroidism	3.5 % (4/114)

Figures in brackets represent number of patients with positive findings over total number evaluated

The prevalence of goiter estimated by ultrasound was 36 % (27/75 patients in whom thyroid volume could be calculated), being more common in females (41 %) than in males (28 %). Nodules greater than 5 mm in diameter (even with normal thyroid volume) were present in 37 out of 81 patients (45.7 %). Multiple nodules were detected in 22 (59.5 %) of them. A solitary thyroid nodule was found in the remaining 15 patients (40.5 %).

Thirty-five percent of patients who showed thyroid nodules (13/37) had positive autoimmunity; elevated thyroid antibodies were also present in 44.4 % of patients in whom thyroid volume was increased (including those without nodules).

There was no significant association between the presence of thyroid nodules and levels of IGF-1 (ULN-IGF-1: median 250 %, range 200–1000 %; n = 103) ($p = 0.805$), duration of the disease ($p = 0.460$) or age ($p = 0.670$).

Eighteen out of the 114 patients (15.8 %) had abnormal functional tests. In 14 patients (12.3 %) primary hypothyroidism was found, in 12 of them accompanied by the presence of positive thyroid autoimmunity (85.7 %). Four out of 114 (3.5 %) had primary hyperthyroidism although none of them had abnormally elevated thyroid antibodies.

Discussion

In this series of patients with acromegaly we found a high frequency (25 %) of thyroid auto-antibodies compared with the prevalence in the normal Argentinean population (10 %), showing a significant statistical difference between the two groups. This frequency is also higher than that found in other studies like the National Health and Examination Survey (NHANES III) which showed in an American thyroid disease free population of 16,533 subjects a prevalence of positive TPOAb of 11.3 % and of TgAb of 10.4 % [12]. In a multicenter Italian study published by Gasperi et al. [5] in 2002 involving 258 acromegalic patients the authors found an elevated prevalence of TPOAb (23 %) and TgAb (21 %), similar to that found in their control group composed by

patients with non-functioning and prolactin secreting pituitary adenomas (21 % for TPOAb and 26 % for TgAb) but they did not make reference to the frequency in the general Italian population. The Japanese study of Ishibashi et al. [6] published in 1991 evaluated 63 acromegalic patients showing only 6.3 % positivity for TgAb and 7.9 % for thyroid microsomal antibodies evaluated by an indirect agglutination technique. Other studies with small number of patients also found a low prevalence of antibodies in acromegaly. Cannavo et al. [7] found only 7 % positivity for TPOAb in 28 acromegalic Italian subjects. Rogozinsky et al. [8] also found a low prevalence of 9 % for TPOAb in 34 Argentinean acromegalic patients involved in their study.

Acromegaly is frequently associated with the presence of thyroid disorders, particularly goiter, although the exact prevalence is uncertain. In acromegaly, goiter has usually been described as nodular, but diffuse goiter may also occur [13]. It is well known that the prevalence of goiter is higher in acromegalic patients than in the general population, with reported figures between 25 and 71 % by palpation and as high as 92 % with ultrasound studies [5, 11]. In our patients, the prevalence of goiter by ultrasound was 36 %, being more common in women than in men. Even when ultrasonography is used, the cutoff to define a goitrous gland remains on debate and this is related to ethnical, sexual and iodine diet content differences around the world [14].

The pathogenesis of goiter in acromegaly has not been completely elucidated. The role of TSH in goiter development is contentious. Normally, TSH plays a major role in thyroid growth, but in acromegaly the correlation between TSH and goiter is controversial. Lack of correlation between TSH levels and thyroid volume has been shown in different series [7, 15]. On the other hand, Tita et al. [16] have reported that TSH and IGF1 levels are known to act synergistically on thyroid cell growth in vitro, increasing the mitogenic and anti-apoptotic action of IGF1 [17]. We found a high percentage (44 %) of thyroid antibodies in our goitrous acromegalic patients, even higher than the already high 25 % figures in the total study population. Besides, although we lack reference data concerning the Argentinean population, the frequency of thyroid dysfunction in our acromegalic patients seems to be higher than that reported by other authors [7]. This finding as well as the high percentage of thyroid autoimmunity could help to explain the development of thyroid morphological alterations.

In our population of acromegalic patients 45.7 % had thyroid nodules by ultrasound, with multiple nodules in most of them (59.5 %). In this group of patients the frequency of thyroid autoimmunity was 35.1 %, considerably higher than in the total population of acromegalic patients (25 %) and also than in the general Argentinean population (10 %).

Cannavó et al. [7] reported thyroid enlargement and thyroid nodularity in 78 and 50 % of the acromegalic population respectively, but failed to demonstrate a significant correlation between thyroid volume and serum GH, IGF1 or TSH values. Similarly, in our study there was no correlation between the presence of thyroid nodules and IGF1 levels, duration of the disease or age.

Several factors such as genetic, hormonal, infectious, anatomical changes and damage of tissue due to inflammation, ischemia or trauma can change the immune system response and cause autoimmune disease, thus changing the prevalence of these diseases in different populations. The role of thyroid autoimmunity in the pathogenesis of thyroid diseases in acromegalic patients is still controversial. The higher frequency of thyroid autoimmunity shown in our acromegalic patients may be an important etiopathogenic factor in the development of thyroid disorders. In the last years increasing evidence has grown in the study of the immuno-modulator effect of GH and IGF-1 on thymus T-cells maturation. GH has proven to have a stimulatory effect on thymus epithelium proliferation and differentiation and in the production of cytokines necessary for T-cells maturation [17, 18]. This could contribute to explain the potential association between both disorders, but we still need more evidence to make a clear conclusion about this issue. In the context of immuno neuroendocrine cross talk, GH stimulates the immune system. The increase in number and migration of lymphocytes described in mice [19] could be involved in the development of thyroid autoimmunity in the context of GH excess.

The development of goiter has been suggested to be a potential mechanism for the increased incidence of thyroid autoimmunity in iodine deficient areas through the over exposition of the immune system to thyroid antigens, leading to humoral and T cell-mediated reactions [20]. As pointed out previously, acromegaly is associated with an increased prevalence of goiter and this may be partially linked to the increased incidence of autoimmunity in this disease.

In the general population the presence of positive thyroid antibodies carries the risk of developing overt hypothyroidism of around 0.2–1 %, depending on baseline TSH [21]. It has to be evaluated if the risk is higher in patients with acromegaly. In accordance with our findings, we suggest measurement of TSH, free T4 and ATPO in patients with acromegaly. The presence of a higher prevalence of anti-thyroid antibodies in patients with acromegaly found in this study allows us to suggest the study of autoimmunity for patients with acromegaly, with the biochemical and anatomical evaluation that has been already recommended [22]. In addition, thyroid US is recommended due to the association with thyroid cancer in acromegaly [23], especially when there is palpable thyroid nodularity [22].

In conclusion, the present study shows a high prevalence of thyroid autoimmunity in acromegaly. Among other

pathogenic mechanisms, autoimmunity seems to be an additional factor inducing a high frequency of thyroid disorders in this pituitary disease.

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Compliance with Ethical Standards

Conflict of interest Marcos Manavela is a Medical Advisor in Novartis. The rest of the authors declare no conflict of interest.

References

1. Eskildsen PC, Kruse A, Kirkegaard C (1988) The pituitary-thyroid axis. Horm Metab Res 20:755–757
2. Carmina E, Rosato F, Pirronello S, Janni A (1983) Hypothalamic-pituitary-thyroid axis in acromegaly. J Endocrinol Invest 6:263–266
3. Uchoa HB, Lima GA, Correa LL, Vidal AP, Cavallieri SA, Vaisman M, Buescu A, Gadelha MR (2013) Prevalence of thyroid diseases in patients with acromegaly: experience of a Brazilian Center. Arq Bras Endocrinol Metabol 57(9):685–690
4. Hegedus L, Perrild H, Poulsen LR, Andersen JR, Holm B, Schnohr P, Jensen G, Hansen JM (1983) The determination of thyroid volume by ultrasound and its relationship to body weight, age and sex in normal subjects. J Clin Endocrinol Metab 56:260–263
5. Gasperi M, Martino E, Manetti L, Arosio M, Porretti S, Faglia G, Mariotti S, Colao AM, Lombardi G, Baldelli R, Camanni F, Liuzzi A, Acromegaly Study Group of the Italian Society of Endocrinology (2002) Prevalence of thyroid diseases in patients with acromegaly: results of an Italian multi-center study. J Endocrinol Invest 25:240–245
6. Ishibashi M, Kuzuya N, Sawada S, Kitamura K, Kamoi K, Yamaji T (1991) Anti-thyroid antibodies in patients with hyperprolactinemia. Endocrinol Jpn 38(5):517–522
7. Cannavo S, Squadrito S, Finocchiaro MD, Curtò L, Almoto B, Vieni A, Trimarchi F (2000) Goiter and impairment of thyroid function in acromegalic patients: basal evaluation and follow-up. Horm Metab Res 32:190–195
8. Rogozinski A, Furioso A, Glikman P, Junco M, Laudi R, Reyes A, Lowenstein A (2012) Thyroid nodules in acromegaly. Arch Bras Endocrinol 56(5):300–304
9. Brunn J, Block U, Ruf G, Bos I, Kunze WP, Scriba PC (1981) Volumetric analysis of thyroid lobes by real-time ultrasound. Dtsch Med Wochenschr 106(41):1338–1340
10. Knudsen N, Bols B, Bulow I, Jorgensen T, Perrild H, Ovesen L, Laurberg P (1999) Validation of ultrasonography of the thyroid gland for epidemiological purposes. Thyroid 11:1069–1074
11. Niepomniszcze H, Pitoia F, Katz S, Chervin R, Bruno OD (2002) Primary thyroid disorders in endogenous Cushing's syndrome. Eur J Endocrinol 147:305–311
12. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, Braverman LE (2002) Serum TSH, T4, and thyroid antibodies in the United State's population (1988–1994): National Health and Nutrition Examination Survey (NANHES III). J Clin Endocrinol Metab 87(32):489–499
13. Colao AM, Auriemma RS, Pivonello R, Galdiero M, Lombardi G (2008) Medical consequences of acromegaly: What are the effects of biochemical control? Rev Endocr Metab Disord 9:21–31
14. Barrere X, Valeix P, Preziosi P, Bensimon M, Pelletier B, Gallan P, Hercberg S (2000) Determinants of thyroid volume in healthy French adults participating in the SU.VI.MAX cohort. Clin Endocrinol (Oxf) 52(3):273–278
15. Herrmann BL, Baumann H, Janssen OE, Görges R, Schmid KW, Mann K (2004) Impact of disease activity on thyroid diseases in patients with acromegaly: basal evaluation and follow-up. Exp Clin Endocrinol Diabetes 112:225–230
16. Tita P, Ambrosio MR, Scollo C, Carta A, Gangemi P, Bondanelli M, Vigneri R, Degli Uberti EC, Pezzino V (2005) High prevalence of differentiated thyroid carcinoma in acromegaly. Clin Endocrinol 63:161–167
17. Smaniotto S, Martins-Neto AA, Dardenne M, Savino W (2011) Growth hormone is a modulator of lymphocyte migration. NeuroImmunoModulation 18(5):309–313
18. Savino W, Postel-Vinay MC, Smaniotto S, Dardenne M (2002) The thymus gland: a target organ for the growth hormone. Scand J Immunol 55(5):442–452
19. Savino W, Smaniotto S, Mendes-da-Cruz DA, Dardenne M (2012) Growth hormone modulates migration of thymocytes and peripheral T cells. Ann N Y Acad Sci 1261:49–54
20. Aghini-Lombardi F, Antonangeli L, Martino E, Vitti P, Maccherini D, Leoli F, Rago T, Grasso L, Valeriano R, Balestrieri A, Pinchera A (1999) The Spectrum of thyroid disorders in an iodine- deficient community: the pescopagano survey. J Clin Endocrinol Metab 84:561–566
21. Walsh JP, Bremner AP, Feddema P, Leedman PJ, Brown SJ, O'Leary P (2009) Thyrotropin and thyroid antibodies as predictors of hypothyroidism: a 13-year, longitudinal study of a community-based cohort using current immunoassay techniques. J Clin Endocrinol Metab 95(3):1095–1104
22. Katznelson L, Laws ER, Melmed S, Molitch ME, Hassan Murad M, Utz A, Wass JAH (2014) Acromegaly: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 99(11): 3933–3951
23. Tita P, Ambrosio MR, Scollo C, Carta A, Gangemi P, Bondanelli M, Vigneri R, Degli Uberti EC, Pezzino V (2005) High prevalence of differentiated thyroid carcinoma in acromegaly. Clin Endocrinol (Oxf) 63(2):161–167