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THYROID DISORDERS IN PATIENTS WITH ACROMEGALY IN BASRAH CITY

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ABSTRACT : Acromegaly is a rare chronic metabolic disorder of adults caused by excessive production of growth hormone and hence more production of insulin-like growth factor 1 (IGF–1). The purpose of present study is to estimate the prevalence of thyroid disorders in patients with acromegaly and their changes according to treatment modalities, assessment the effect and correlation of GH and IGF–1 level with the levels of TSH, TT4, FT4 and TT3 and evaluation the status of TG in patients regarding the levels of GH, IGF–1 and treatment modalities. The cross-sectional study included 59 patients with acromegaly (31 female (52.5%) and 28 male (47.5%); mean age: 45.80±12.58 years), who are regular attendants to FDEMC between August 2019 and February 2020. All patients have active GH secreting pituitary adenomas (16 had microadenoma). In conclusion, high prevalence of thyroid disorders in patients with acromegaly. Thyroglobulin level was elevated in patients with acromegaly especially when it is uncontrolled. Total T4 are significantly increased in patients with acromegaly and serum GH and IGF–1 level in acromegaly had no significant correlation with TSH, FT4, TT3 and Tg levels.

Key words : Acromegaly, thyroid disorders, thyroglobulin.

INTRODUCTION

Acromegaly is a rare chronic metabolic disorder of adults caused by excessive production of growth hormone and hence more production of insulin-like growth factor 1 (IGF–1). The underlying cause of most cases has been revealed to be micro–or macro–adenoma of anterior pituitary gland. (Melmed, 2017). A recent study in southern of Iraq showed that the GH–secreting adenoma was the most common adenoma (Mansour *et al*, 2018) with a prevalence of 8.2 people per million and 5.3 patients per million occurred annually was showed in a study from the northern of Iraq (Qasim, 2017). It often diagnosed late (4 to 10 years of onset) and equally effected on both sexes (Lavrentaki *et al*, 2017). Thyroid diseases are frequently seen in patients with acromegaly. Many studies from different countries showed different results for the prevalence of thyroid autoantibodies in acromegalic patients. In addition to, hypothyroidism found to be the common thyroid disorder associated with acromegaly rather than hyperthyroidism (Manavela *et al*, 2015; Natchev *et al*, 2020).

Due to the limited studies that reveal these issues in acromegalic patients in Basrah, our study tries to estimate the Prevalence of thyroid disorders in patients with acromegaly and their changes according to treatment modalities, assessment the effect and correlation of GH and IGF–1 level with the levels of TSH, TT4, FT4 and TT3 and evaluation the status of TG in patients regarding the levels of GH, IGF–1 and treatment modalities.

MATERIALS AND METHODS

Our cross-sectional study involved fifty–nine patients with acromegaly (31 female (52.5%) and 28 male (47.5%); mean age: 45.80±12.58 years), who are regular attendants to FDEMC. All patients have active GH secreting pituitary adenomas (16 had microadenoma), their diagnosis was established through combined positive GH under oral glucose tolerance test (OGTT) with neuroimaging study specifically pituitary directed MRI showing results consistent with the diagnosis of acromegaly. All patients were assessed for signs and symptoms of thyroid diseases after written informed consent was signed, according to a protocol approved by the Ethics Committee of the Health and Medical Technical College, Southern Technical University. Serum GH, TSH, TT4, TT3, FT4, TG, TgAb and TPO Ab levels were determined using Roche kits. These measurements were performed using the electrochemiluminescence immunoassay "ECLIA" method in analysis. Serum IGF-1 level was determined by using DRG company kit which using the enzyme linked immunosorbent assay (ELISA)

method in analysis. The normal range for serum TSH, TT4, TT3, FT4, TG, TgAb and TPO Ab is (0.270 – 4.20 µIU/mL, 5.1 – 14.1 µg/dL, 0.8 – 2.0 ng/ml, 0.93 – 1.7 ng/dL, 3.5 – 77 ng/mL, < 115 IU/mL, < 34 IU/mL, respectively). Serum IGF-1 levels were compared to reference levels normalized for age. Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) Version 26.0 software package. The data are presented as mean ± SD, with minimum and maximum as range. Independent samples T–test used for comparison between continuous data and Values of ($p < 0.05$) were considered statistically significant.

RESULTS

According to disease activity, we divided the patients into two groups; first group consisted of patients with controlled acromegaly (n=27), 12 males (44.4%) and 15 females (55.6%), and the second group consisted of uncontrolled patients (n=32), 16 males (50.0%) and 16 females (50.0%). Table 1 shows thyroid parameters abnormalities in patients with acromegaly, where it shows that most of the studied patients 59.3% (35/59) have normal TSH, FT4, TT4, TT3 as well as thyroglobulin (93.3%, 91.6%, 98.4%, 93.3% and 77.9%, respectively) and hence are labelled as completely euthyroid. The remaining 40.7% of the studied patients had at least one of the thyroid parameters was abnormal and mostly abnormality in the thyroglobulin level, as well thyroid hormones abnormalities are usually on the low side rather than the high side. Statistically, there is a significant association ($p < 0.05$) in that thyroid disorders are prevalent in acromegalic patients.

There are three patients, who had more than one thyroid parameter abnormality, one had high thyroglobulin with suppressed TSH and considered as subclinical hyperthyroidism, the other one had both low TT3 and FT4 and considered as having central hypothyroidism and the last had both low TSH and TT3 and considered as having also central hypothyroidism. Comparison between controlled and uncontrolled studied patients for the levels of thyroid parameters in Table 2 shows only one significant difference ($p < 0.05$) in the level of TT4 between the two groups.

Despite there is numerical difference in the levels of TSH, FT4, TT3 as well as the thyroglobulin levels towards hyperthyroidism status (1.58 ± 0.71 µIU/ml, 1.15 ± 0.15 ng/dl, 1.10 ± 0.18 ng/ml, 31.59 ± 62.12 ng/ml in the controlled group versus 1.40 ± 1.07 µIU/ml, 1.24 ± 0.24 ng/dl, 1.22 ± 0.32ng/ml, 43.87 ± 91.59 ng/ml in the uncontrolled group), none had shown statistical significance (p 0.44; 0.07; 0.09; 0.54 for TSH, TT3, FT4 and thyroglobulin, respectively) in the uncontrolled group in comparison to the controlled group.Twelve patients (20.3%) out of fifty–nine patients showed elevated titers of autoantibodies (Table 3). Among all patients with positive autoimmunity halve of them were women, mean age 54 years (45–64 years) and the other halve were men, mean age 41 years (26–57 years), six of these patients were found in the control group and the other six found within the uncontrolled group. Positive TPO Abs was found in 9(15.3%) and positive Tg Abs found in 8(13.6%) among involved patients.

Table 1 : Thyroid parameter abnormalities in patients with acromegaly.

Variables	Mean±SD	Low	Normal	High
		No. (%)		
TSH (µIU/ml)	1.49 ± 0.92	3 (5.1)	55 (93.3)	1 (1.6)
FT4 (ng/dl)	1.20 ± 0.21	4 (6.8)	54 (91.6)	1 (1.6)
TT4 (ug/dl)	8.39 ± 2.09	0 (0.0)	58(98.4)	1 (1.6)
TT3 (ng/ml)	1.16 ± 0.27	3 (5.1)	55 (93.3)	1 (1.6)
Thyroglobulin (ng/ml)	38.25 ± 79.07	6 (10.2)	46 (77.9)	7 (11.9)
All Disorders	Normal		Abnormal	
	35 (59.3)		24 (40.7)	

Table 2 : Thyroid hormones according to the degree of GH and IGF–1 by GH and IGF–1 estimation.

Variables	Controlled patients	Uncontrolled patients	*P*-value
	Mean ± SD	Mean ± SD	
TSH (µIU/ml)	1.58 ± 0.71	1.40 ± 1.07	0.44
FT4 (ng/dl)	1.15 ± 0.15	1.24 ± 0.24	0.09
TT4 (ug/dl)	7.77 ± 1.40	8.92 ± 2.43	0.02
TT3 (ng/ml)	1.10 ± 0.18	1.22 ± 0.32	0.07
Thyroglobulin (ng/ml)	31.59 ± 62.12	43.87 ± 91.59	0.54

Table 3 : Frequency of thyroid autoantibodies, hypothyroidism and hyperthyroidism in 59 patients with acromegaly.

Thyroid alteration	Acromegalic patients (%)
Positive autoantibodies	20.3% (12/59)
Hypothyroidism	37.5%(22/59)
Hyperthyroidism	1.6% (1/59)

About (37.5%) of our patients had hypothyroidism (20.8% had primary hypothyroidism, where 4.2% was subclinical primary hypothyroidism, and 16.7% had central hypothyroidism), while only (1.6%) of patients had subclinical hyperthyroidism.

DISCUSSION

Our study showed about (37.5%) of acromegalic patients had hypothyroidism and only (1.6%) had

hyperthyroidism with 20.3% of patients showed positive thyroid autoantibodies. Several studies have found a low prevalence of hyperthyroidism and varied frequency of hypothyroidism associated with acromegaly (Mukhtar *et al*, 1971; Tita *et al*, 2005; Manavela *et al*, 2015; Natchev *et al*, 2020), most of these studies are in agreement with our results in respect to the difference in the number of patients involved. Other studies by Cannavo *et al* (2000), Gasperi *et al* (2002) and Wu *et al* (2018) reported hypothyroidism was found in (26%, 4.7% and 7% in respectively) among their patients. The current study indicates 20.3% (12/59) had thyroid autoantibodies. Previous studies by Manavela *et al* (2015), noted 25% of patients had autoantibodies. In addition, Gasperi *et al* (2002), showed 23% of patients had TPO Abs and 21% had Tg Abs. While, Cannavo *et al* (2000), reported positive TPO Abs in 7% of 28 patient. Rogozinsky *et al* (2012) found only 9% out of 34 Argentinian acromegalic patients had positive TPO Abs. It seems possible that these results are due to increasing evidence for the effect of GH and IGF–1 on the immune response where it has been proved that GH and IGF–1 can stimulate T–cell maturation in thymocyte and partially due to the prevalence of goiter in acromegalic patients (Manavela *et al*, 2015). The serum TG concentration was elevated in 11.9% (7/59) of the acromegalic patients. The production and secretion of TG regulated by TSH (Errick *et al*, 1985; Van Herle *et al*, 1979). Although, TG release in normal subjects can be stimulated by exogenous TSH (Unger *et al*, 1980). Miyakawa *et al* (1988) observed elevation in serum TG concentration in 50% of involved patients. The effect of TSH on goiter formation is expressed in the first years of acromegaly, while in the next stage, thyroid tumorigenesis becomes independent, or at least less dependent on TSH (Cheung *et al*, 1996; Cheung and Boyages, 1997). Wu *et al* (2018) study showed a positive correlation between the random GH, IGF–1, with thyroid volume.Some studies showed a successful surgical removal of somatotropinoma, or medical treatment with somatostatin analogs lead to normalization of IGF–1 level and result in a decrease in thyroid volume, by up to 25% (Cheung and Boyages, 1997; Herrmann *et al*, 2004; Miyakawa *et al*, 1988). However, somatostatin analogs receptors in the thyroid tissue are independently influence on thyroid volume, this should be taken into consideration (Ain and Taylor, 1994; Boy *et al*, 2011; Cheung and Boyages, 1997). It is interesting to note that there is difference in TG level between controlled and uncontrolled groups, however it does not reach statistical significance, this in agreement with the results founded by Miyakawa *et al* (1988). Seven patients found with high TG level are classified within uncontrolled group where the IGF–1 level is high and one of them have been associated with multinodular goiter. While other six patients showed low level of TG and classified within controlled group, these six patients have been underlying trans–sphenoidal surgery and treatment, one of those six patients had multinodular goiter and have been underlying thyroidectomy.A possible explanation for this might be that TG synthesis and secretion is regulated by many factors and IGF–1 play partial role. According to our finding, there is no significant correlation between GH, IGF-1 level with the levels of thyroid parameters except for TT4. These findings further support the study from china by Yu and HU (2017) that reported a significant difference in TT4 between the groups with high and low IGF–1 level, negative correlation with TSH and no correlation with FT4 and TT3. Wu *et al* (2018) observed a tendency of lower TSH level and higher FT4 and TT3 levels in the group of high GH concentration but no significant difference in TSH, FT4, TT4 and TT3 found between the groups dividing according to the level of GH.In parallel with our finding, Kan *et al* (2019), study in Turkey showed no significant difference in TSH and FT4 between the studied groups after divided according to the activity of disease. But our results conflict with Zhang *et al* (2018), which found no significant difference in TSH, TT4, FT4 and TT3 between cured and discordant groups of patients.

CONCLUSION

Our study showed a high prevalence of thyroid disorders in patients with acromegaly. Thyroglobulin level was elevated in patients with acromegaly especially when it is uncontrolled.Total T4 are significantly increased in patients with acromegaly and serum GH and IGF–1 level in acromegaly had no significant correlation with TSH, FT4 and TT3.

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