Original Article

DOI: 10.4274/tjem.3558
Turk J Endocrinol Metab 2016;20:78-82

Relationship between Empty Sella Syndrome and Hashimoto's Thyroiditis

Empty Sella Sendromu ve Hashimoto Tiroiditi Arasındaki İlişki

İdris Kuzu, Sayid Shafi Zuhur*, Alper Özel**, David Ojalvo, Feyza Yener Öztürk, Yüksel Altuntaş

Şişli Etfal Training and Research Hospital, Clinic of Endocrinology and Metabolism, İstanbul, Turkey
*Namık Kemal University Faculty of Medicine, Department of Endocrinology and Metabolism, Tekirdağ, Turkey
**Şişli Etfal Training and Research Hospital, Clinic of Radiology Medicine, İstanbul, Turkey

Abstract

Purpose: It is not clear if Hashimoto's thyroiditis leads to Empty sella syndrome. In the present study, we aimed to investigate if Hashimoto's thyroiditis was associated with Empty sella syndrome, and Hashimoto's thyroiditis was a secondary cause od some cases of primary Empty sella syndrome.
Material and Method: Eighty-one patients who were diagnosed with primary Empty sella syndrome were included in the study. All patients underwent thyroid ultrasonography and biochemical tests for thyroid-stimulating hormone, free triiodothyronine, free thyroxine, anti thyroid peroxidase, anti thyroglobulin, follicle stimulating hormone, luteinizing hormone, 17 β estradiol, growth hormone, insulin-like growth factor 1, adrenocorticotropic hormone and total testosterone for Hashimoto's thyroiditis and pituitary hormone deficiency.
Results: Out of 81 patients, thyroid disease was diagnosed in 34 (42%) patients; 18 of them had Hashimoto's thyroiditis (22.2%) and 16 (19.8%) had central hypothyroidism. Among Hashimoto's thyroiditis patients, 11 (13.6%) had hypothyroidism and 7 (8.6%) were euthyroid.
Discussion: In conclusion, it is possible that some cases of primary Empty sella syndrome are caused by Hashimoto's thyroiditis. It is recommended that the presence of Hashimoto's thyroiditis should be investigated in patients with primary Empty sella syndrome. Further studies investigating anti-pituitary antibody in patients with primary Empty sella syndrome, are needed to further declare this relationship.
Keywords: Primary Empty sella syndrome, Hashimoto's thyroiditis, hypopituitarism

Öz

Amaç: Hashimoto tiroiditi Empty sella sendromuna yol açıp açmadığı konusu açık değildir. Biz bu çalışmada Hashimoto tiroiditinin Empty sella sendromu ile ilişkisi olup olmadığını ve primer Empty sella sendromu olgularından bir kısmına Hashimoto tiroiditinin sekonder bir sebep olup olamadığını araştırmayı amaçladık.
Gereç ve Yöntem: Çalışmaya alınan primer Empty sella sendromu tanısı konan 81 hastaya Hashimoto tiroiditi ve hipofiz hormon eksiklikleri açısından tiroid uyarıcı hormon, serbest triiyodotironin, serbest tiroksin, anti tiroid peroksidaz, anti tiroglobulin, folikül uyarıcı hormon, lüteinleştirici hormon, 17 β estradiol, büyüme hormonu, insülin benzeri büyüme faktörü-1, adrenokortikotrop ve total testosteron biyo-kimyasal tetkikleri ve tiroid ultrasanografi yapıldı.
Bulgular: Çalışmada toplam 81 hastadan 34 tanesinde (%42) tiroid hastalığı saptandı. Bunlardan 18 tanesi Hashimoto tiroiditi (%22,2), 16 tanesi santral hipotiroidi (%19,8) olarak saptandı. Hashimoto tiroiditi olan 18 hastadan 11 tanesi hipotiroidik (%13,6), yedi tanesi (%8,6) ise ötiroid olarak saptandı.
Tartışma: Sonuç olarak idiopatik Empty sella sendrom olgularının bir kısmının Hashimoto tiroiditi aracılığıyla oluşması muhtemeldir. Primer Empty sella sendromlu olgularda Hashimoto tiroiditi varlığı araştırılması önerilir. Bu konuda anipituiter antikorların da bakıldığı daha kapsamlı çalışmalara ihtiyaç vardır.
Anahtar kelimeler: Primer Empty sella sendromu, Hashimoto tiroiditi, hipopitüitarizm

Introduction

Empty sella syndrome (ESS) is an entity in which the sella turcica is filled with cerebrospinal fluid via subarachnoid space herniation, due to compression of the pituitary tissue upto sellar base and walls (1,2). ESS may cause single or more than one pituitary hormone deficiencies at different levels (3). ESS is classified as primary and secondary ESS (4). Secondary ESS may occur due to radiotherapy, surgery, vascular, infective, traumatic, and autoimmune diseases in addition to some causes, such as spontaneously regressed pituitary adenomas or adenomas regressed after medical treatment (4). Primary ESS is a condition which develops without the causes mentioned above and is classified as idiopathic or primary ESS. Some studies proposed that different secondary causes might be present in patients who

Address for Correspondence: İdris Kuzu MD, Şişli Etfal Training and Research Hospital, Clinic of Endocrinology and Metabolism, İstanbul, Turkey
Phone: +90 505 775 64 70 E-mail: idrisskuzu@gmail.com **Received:** 22/02/2016 **Accepted:** 08/06/2016
Turkish Journal of Endocrinology and Metabolism, published by Galenos Publishing.

are accepted as having primary ESS (5). However, if all possible etiologies are ruled out carefully, the frequency of ESS cases that are defined as "idiopathic" may decrease (5). In the present study, we investigated if there was an association between Hashimoto's thyroiditis (HT) and ESS.

Materials and Methods

We evaluated magnetic resonance imaging (MRI) results of a total of 120 patients. 70 patients who were referred to our pituitary diseases outpatient clinic between October 2014 and March 2015 and were diagnosed with primary ESS according to their cranial or pituitary MRI, history and physical examination results, and 50 patients with primary ESS who were enrolled in our previous study (3) were included in the study. All MRI's of the patients were re-evaluated by an experienced radiologist to confirm ESS diagnosis. Patients with a history of congenital or acquired hypothalamic-pituitary diseases, previous pituitary surgery or radiotherapy, a history of head trauma, medical treatment for pituitary adenomas, patients with a prolactin levels higher than 100 ng/mL (in whom the presence of a prolactinoma could not be ruled out), patients who was diagnosed with Sheehan's syndrome, and patients with primary adrenal or gonadal insufficiency were not included in the study. A total of 81 patients with the diagnosis of primary ESS were included in the study. Anterior pituitary deficiency and possible HT were evaluated by physical examination, ultrasonography (USG), and biochemical analysis.

Imaging Studies

The anatomical integrity of the hypothalamo-pituitary region of all of the subjects was evaluated by MRI. All MRI's of the subjects were evaluated and/or revised by an experienced radiologist who was blind to the laboratory data and clinical condition of the subjects. The diagnosis of primary ESS was considered in the presence of intrasellar cerebrospinal fluid with a thinned pituitary

Table 1. Frequencies of thyroid disease in patients with primary empty sella syndrome

	Number	Percentage (%)
Non-HT	63	77.8
HT	18	22.2
Hypothyroid HT	11	13.6
Euthyroid HT	7	8.6
Central hypothyroidism	16	19.8

HT: Hashimoto's thyroiditis

Table 2. Patients with Hashimoto's thyroiditis among cases with primary empty sella syndrome

No	Age	Gender	Height	Weight	BMI	DM	HT*	TSH	fT_3	fT_4	Anti TPO	Anti-TG	Thyroid USG	HT
1	65	F	157	52	21.1	+	+	1.27	3.11	1.12	+	+	+	Euthyroid
2	44	F	164	78	29	-	-	2.24	2.58	1.55	+	+	+	Euthyroid
3	43	F	154	86	36.2	+	+	5.88	2.61	1.02	-	+	+	Hypothyroid
4	66	M	175	90	29.3	-	-	7.16	2.61	0.92	-	+	+	Hypothyroid
5	74	F	148	70	32	-	+	4.9	3.02	1	+	+	+	Hypothyroid
6	72	F	176	85	27.4	-	-	5.23	2.76	0.89	+	-	+	Hypothyroid
7	30	F	161	77	29.7	-	-	8.18	2.90	1.04	+	-	+	Hypothyroid
8	52	F	158	101	40.4	-	-	4.80	3.41	0.96	+	+	+	Hypothyroid
9	38	F	155	66	27.4	-	-	4.73	3.09	0.98	-	+	+	Hypothyroid
10	36	F	156	48	19.7	-	-	3.05	2.94	1.1	+	+	+	Euthyroid
11	53	M	174	89	29.4	-	-	5.35	3.14	0.91	+	+	+	Hypothyroid
12	46	F	157	87	35.3	+	-	4.88	2.61	1.02	-	+	+	Hypothyroid
13	51	M	156	90	37	-	-	21	2.24	0.76	-	+	+	Hypothyroid
14	37	F	161	90	34.7	-	+	2.98	2.72	1.11	-	+	+	Euthyroid
15	35	M	175	98	32	-	-	1.61	3.52	1.23	+	-	+	Euthyroid
16	55	F	162	92	35	+	+	5.08	2.34	1.19	+	+	+	Hypothyroid
17	34	F	160	83	32.4	-	-	2.52	2.59	1.05	+	+	+	Euthyroid
18	45	M	165	78	28.6	-	-	1.15	2.88	0.95	-	+	+	Euthyroid

*Hypertension, TSH: Thyroid-stimulating hormone, HT: Hashimoto's thyroiditis, USG: Ultrasonography, DM: Diabetes mellitus, fT3: Free triiodothyronine, fT4: Free thyroxine, BMI: Body mass index, F: Female, M: Male, Anti-TG: Anti-thyroglobulin

Normal reference values: TSH: 0.27-4.5, uIU/mL, fT_4: 0.8-1.67 ng/dL, fT_3: 1.64-4.42 pg/mL; anti peroxidase: 0-35 IU/mL, Anti thyroglobulin: 0-115 IU/mL

gland flattened against the sellar floor (1). All MRIs were performed by means of a 1.5 Tesla superconducting magnet (Siemens Avanto, Siemens, Erlangen, Germany) with multiple sagittal and coronal planes on T1 sequences with/without gadolinium. All USG examinations of the thyroid were performed by the same radiologist. A color Doppler USG device (Toshiba, Aplio XV, Tokyo, Japan) equipped with a 7- to 14-MHz wide-band linear transducer was used. The USG criteria suggesting HT were diffuse hypoechoic enlargement, patchy ill-defined hypoechoic areas separated by echogenic fibrous septa, and micro nodular pattern involving the whole gland (6,7).

Laboratory Analysis

Venous fasting blood samples were obtained from each patient in the morning between 08:00 a.m. and 09:00 a.m. The samples were studied without any delay for serum thyroid-stimulating hormone (TSH), free triiodothyronine (fT_3), free thyroxine (fT_4), anti thyroid peroxidase (antiTPO), anti thyroglobulin (antiTG), prolactin, follicle stimulating hormone (FSH), luteinizing hormone (LH), cortisol and 17 β estradiol levels. Serum TSH, fT_3, fT_4, antiTPO, antiTG, prolactin, FSH, LH, cortisol, and 17 β estradiol levels were assessed by electrochemiluminescence immunoassay method using cobas immunoassay analyzers (Roche Diagnostics GmbH, Mannheim, Germany); and serum growth hormone, insulin-like growth factor 1, adrenocorticotropic hormone and total testosterone levels were assessed by Immulite 2000 assay (Siemens AG, Munich, Germany). HT was diagnosed if the patients had antiTPO >35 IU/mL and/or antiTG >115 IU/mL and USG results consistent with HT. In addition to the above diagnostic criteria, patients were diagnosed with hypothyroid HT if their TSH levels were >4.5 uIU/mL. Patients were diagnosed as having central hypothyroidism if TSH values were within the normal reference limits or <0.27 uIU/mL in addition to fT_4<0.8 ng/dL and/or fT_3<1.64 pg/mL. Patients with and without HT were compared in terms of hypertension, diabetes mellitus (DM), age, height, body weight, and body mass index (BMI).

Statistical Analysis

Statistical analysis was performed by using SPSS (Statistical Package for Social Sciences for Windows, release 22.0.0 standard version; SPSS Inc, NY, USA). Nominal data were presented as percentages and numeric data were presented as mean ± standard deviation. Patients with and without HT were compared in terms of age, height, weight, and BMI, by using two-sample t-test. Gender, DM, and hypertension were compared between patients with and without HT by chi-square test. The level of significance was accepted as p<0.05.

Results

In the present study, thyroid disease was diagnosed in 34 out of 81 (42%) patients in whom 18 (22.2%) had HT and 16 (19.8%) had central hypothyroidism (Table 1). In patients with HT, 11 (13.6%) had hypothyroidism and 7 (8.6%) were euthyroid (Table 1). Ten patients with HT (55.5%) were newly diagnosed and 8 (44.5%) were previously diagnosed. No significant difference was determined in terms of age, height, BMI, gender and hypertension between primary ESS patients with and without HT (p=0.99, p=0.27, p=0.11, p=0.93 and p=0.52, respectively). Although the frequency of DM was higher in HT patients, no statistically significant difference was determined (p=0.08). HT was observed in none of primary ESS patients with central hypothyroidism. The patient characteristics for those with primary ESS and HT and their descriptive statistical data are presented in Tables 2 and 3, respectively. Among primary ESS patients, 12 (14.8%) had hyperprolactinemia; 16 (19.7%) had central hypothyroidism, 22 (27.1%) had gonadotropin deficiency; 20 (24.6%) had GH deficiency, and 6 (7.4%) had cortisol deficiency. The diagnosis of different anterior pituitary hormone deficiencies was performed according to the relevant guidelines.

Table 3. Patient characteristics in their descriptive statistical data

	Presence of HT	n	Mean ± standard deviation	1. quartile (25%)	Median (50%)	3. quartile (75%)	p
Age	Without HT	63	48.65±14.65	40	47	56	0.99
	With HT	18	48.66±3.42	36.75	45.50	57.50	
Height	Without HT	63	159.85±6.55	155	159	165	0.27
	With HT	18	161.88±8.20	156	160.5	167.25	
Weight	Without HT	63	72.36±14.04	63	74	81	0.02
	With HT	18	81.11±4.36	75.25	85.5	90	
BMI	Without HT	63	28.51±5.79	25.3	28	32.5	0.11
	With HT	18	30.92±5.26	28.3	30.85	35.07	
TSH	Without HT	63	1.70±1.32	0.76	1.5	2.19	0.00
	With HT	18	5.11±4.42	2.45	4.84	5.48	
fT_3	Without HT	63	2.57±0.80	2.14	2.73	3.12	0.18
	With HT	18	2.83±0.34	2.6	2.82	3.09	
fT_4	Without HT	63	1.01±0.34	0.75	1.09	1.26	0.73
	With HT	18	1.04±0.16	0.94	1.02	1.11	

TSH: Thyroid-stimulating hormone, BMI: Body mass index, HT: Hashimoto's thyroiditis, fT_3: Free triiodothyronine, fT_4: Free thyroxine

Discussion

Different etiologies may be present among patients diagnosed with primary ESS (5). García-Centeno et al. (8) reported HT frequency as 26.7% among primary ESS patients (9). In the present study, the frequency of HT was 22.2% among primary ESS patients. This ratio was higher than HT prevalence (0.3-1.2%) in the general population (9,10,11,12,13). These results show that there is a relationship between HT and primary ESS.

Studies suggested an association between LH and autoimmune thyroiditis (AT) because of the similar pathological processes between LH and AT (14,15,16,17,18,19,20). It has been shown that the anti-pituitary antibody positivity rate was between 10% and 20% in HT (15,21,22). Manetti et al. (15) reported that 11.4% of 961 patients with autoimmune thyroid diseases were positive for anti-pituitary antibodies and ESS developed in approximately 10% of LH cases (23,24). LH develops due to immune mediated chronic inflammation of the pituitary gland. LH is the potential cause of idiopathic ESS because of subsequent atrophy and fibrosis following increase in pituitary gland size (23). It is quite difficult to diagnose LH. Clinical, laboratory and imaging studies are used to diagnose LH. However, none of these diagnostic methods are specific for the diagnosis of LH (23). Since it is not always possible to perform a biopsy of the pituitary gland in all suspected cases with LH or to measure anti-pituitary antibody levels, the diagnosis is generally based on exclusion of other diseases of the pituitary gland (25). Moreover, the sensitivity (20-30%) of the anti-pituitary antibody is limited in LH (21,26,27,28). As a result, AT or HT might accompany LH development, and since the diagnosis of LH is difficult, it could not be diagnosed most of the time; the condition manifest finally itself as ESS (24). Anti-pituitary antibody positivity has been determined in 22-42% of cases of primary ESS (23,28). In our study, some of the ESS cases may have been developed due to LH and LH may has accompanied HT. LH and HT may be coexisting diseases with different onset or/and progression times, but at the end, both may result in atrophy of their originating glands. Finally, LH may result in reduction of the size of the pituitary parenchyma and progress to ESS and hypofunction of the thyroid gland.

It has also been reported that ESS might develop in primary hypothyroidism (29,30). This condition is thought to be due to regression of secondary pituitary hyperplasia developing secondary to peripheral zone gland deficiency after starting levothyroxine treatment (29,30). There are case reports showing that ESS may develop after the increase of pituitary size related to primary hypothyroidism, and subsequent regression of pituitary size after levothyroxine treatment (31,32). Moreover, development of LH has been reported in patients with malignant melanoma after treatment with an anti cytotoxic T-lymphocyte associated protein-4 antibody ipilimumab (33,34), however, none of the participants in this study received such a treatment. The limitation of our study is that we could not measure anti-pituitary antibody levels. However, current diagnostic methods have limited clinical value for determination of anti-pituitary antibodies. It has been reported that sensitivity of anti-pituitary antibodies for the diagnosis of LH was between 20% and 70% (21,26,27,28).

Conclusion

In conclusion, as it is difficult to diagnose LH and LH, diagnosis may be often missed and final outcome may manifests as ESS. Nevertheless, LH may be an autoimmune process accompanying HT. LH may coexist with HT and may be the cause of some of the primary ESS cases. Therefore, it is recommended that the presence of HT should be investigated in patients with primary ESS. Further studies investigating anti-pituitary antibody in patients with primary ESS are needed to further declare this relationship.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of Şişli Etfal Training and Research Hospital, Informed Consent: The concent form was filled out by all participants of this study.

Peer-review: External and Internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: İdris Kuzu, Sayid Shafi Zuhur, Concept: İdris Kuzu, Design: İdris Kuzu, Sayid Shafi Zuhur, Data Collection or Processing: Feyza Yener Öztürk, Yüksel Altuntaş, Analysis or Interpretation: İdris Kuzu, Literature Search: Alper Özel, David Ojalvo, Writing: İdris Kuzu.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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