THYROID HEMIOGENESIS ASSOCIATED WITH GRAVES' DISEASE: A CASE REPORT AND REVIEW OF THE LITERATURE

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Abstract

Introduction. Thyroid hemiogenesis (TH) is a congenital developmental disorder. Most cases are euthyroid although hyperthyroidism, hypothyroidism, and malignancy may develop. We present a case of hemiogenesis with Graves' disease (GD) and review the literature about the association.

Case report. A 45-year-old female patient was admitted to the endocrinology department due to nausea and diarrhea. Her past medical history revealed hyperthyroidism diagnosed a year ago. On thyroid examination, right thyroid lobe was palpable, but left lobe and isthmus were not. Physical examination involving other organ systems was unremarkable except for fine tremor of the hands. Thyroid function tests revealed a high level of free T4 and T3 with a low serum TSH. Thyroid antibodies were all positive. Left lobe and isthmus were invisible on thyroid ultrasonography (US) and the right thyroid lobe measuring 44x18x12 mm was diffusely heterogeneous in echo texture. Thyroid scan using Technetium-99m showed increased homogeneous tracer uptake in the right lobe. The patient was diagnosed with TH and GD.

Discussion. In case of unilateral increased uptake on scintiscan, GD with hemiogenesis must be kept in mind in the differential diagnosis of autonomous solitary adenoma, postinflammatory atrophy of thyroid in Hashimoto's disease, focal or unilateral subacute thyroiditis, and primary or metastatic carcinoma. It is prudent to do thyroid ultrasound along with scintigram. US is a valuable tool for the quick diagnosis of TH and differential diagnosis from other causes.

Key words: Throid hemiogenesis, Graves' disease.

INTRODUCTION

Thyroid hemiogenesis (TH) is a rare developmental disorder of the thyroid gland. Since the majority of cases are asymptomatic, the actual incidence is unknown. Nevertheless the reported incidence in the literature varies between 0.05% and

0.07% (1). Although most of the cases are euthyroid, TH may be associated with hyper- or hypothyroidism. Euthyroid cases can be easily missed if they are not already evaluated about thyroid disorders. Besides it is possible to misdiagnose TH with thyrotoxicosis and take wrong approach. Scintiscan of thyroid in TH with thyrotoxicosis may be confused with contralateral suppression due to autonomous solitary nodule, post inflammatory thyroid atrophy due to Hashimoto disease, focal or unilateral sub-acute thyroiditis, and primary or metastatic carcinoma (2).

Although there are plenty of cases regarding thyroid hemiogenesis in the literature, the number of those in association with GD is 50 since 1967. Although, based on our literature search, the very first cases reported in 1967 by Mirouze J *et al.* (one case) (3) and in 1969 by Harada T *et al.* (three cases) (4) in addition to 2 other cases reported by Levy EG (5) (one case) and Rashid HI *et al.* (6) (one case) are herein mentioned, the 6 cases were actually not included into our analysis due to the lack of detailed information.

In this report we present a case of TH associated with Graves' disease (GD) and review the literature about the association and discuss diagnostic methods.

CASE REPORT

A 45 year old female patient was admitted due to nausea and diarrhea for 2 days to the endocrinology clinic. She had a temperature of 36.5°C (97.7°F), blood pressure of 120/70 mmHg, and heart rate of 97 bpm/regular. Fine tremor of the hands was evident on physical examination. Right lobe was palpable while left lobe and isthmus were not. She did not show signs of Graves's ophthalmopathy. Physical examination of the other organ systems was unremarkable. Her past medical history revealed hyperthyroidism one year ago. She denied using any iodine containing drug,

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radiotherapy, and thyroid or head-neck surgery. She did not have any family member with thyroid disease. She was already taking propylthiouracil (PTU) 50 mg bid.

Thyroid function tests revealed a serum thyroid-stimulating hormone (TSH) level of 0.01 μ U/mL (0.35-4.94), free thyroxine (fT4) 1.80 ng/dL (0.7-1.48), free triiodothyronine (fT3) 3.82 pg/mL (1.71-3.71). Thyroid autoantibodies were positive; [TSH receptor antibody (TRAb) 6.1 U/L (>1.5), antithyroid peroxidase antibody (anti-TPO) 99.8 IU/mL (>5.61), and anti-thyroglobulin antibody (antiHTG) 671.7 IU/mL (>4.11)]. Left lobe and isthmus were invisible on thyroid ultrasonography (US). Right lobe was 44x21x16 mm in size with heterogeneous parenchyma echogenicity and nodule was not detected (Fig. 1). Hypervascularity was present. The thyroid scintiscan with 5 mCi Technetium 99m-Per technetate (99mTc) revealed increased homogeneous tracer uptake in the right lobe (6.7%; 0.03-3.75%). Isthmus, pyramidal lobe, and left lobe were not visualized (Fig. 2). The patient was diagnosed with TH and GD. The dose was then adjusted and radioactive iodine (RAI) therapy was planned.

DISCUSSION

TH is a benign, congenital disorder in which one lobe of the thyroid gland fails to develop while the other lobe develops normally with or without an isthmus. Although there are over 300 cases of TH in the literature (7), we detected 50 cases associated with GD since 1967. A total of 6 cases which were included in this count were either written in a language other than English or were lacking a full text. Detailed features of

44 cases involved in our analysis are depicted in Table 1.

First cases in the English literature were reported in 1972 by Harada T *et al.* (8). They presented 7 cases of TH of which five were hyperthyroid. The pathologic examination of one case who had undergone surgery revealed struma parenchymatosa basedowificata. The details of 4 cases were presented in a review written by Ozaki O *et al.* from the same center in 1994 (9). The number of cases reported and knowledge about this subject increased in the following years.

Prevalence of TH is 0.07% in the literature (1) and GD is 0.5% in iodine sufficient areas (10). Data about association of TH with GD is lacking. Since 50 cases in total have been reported in the literature until recently, it is obviously a rare association. In addition hyperthyroidism was reported to be the major clinical presentation of TH (11). The recent review published in 2012 revealed the majority of cases with TH were congenitally hypothyroid and other frequent pathologies of the persistent lobe were hyperthyroidism, hypothyroidism, and goiter (7). Data on age were available in 43 out of 44 patients analysed. Mean age of female was 36 $\pm$ 13 years (8-65) and of male was 41 $\pm$ 17 years (16-65). Although it may occur at any age, women aged between 40-60 years are more likely to develop GD (12). Mean age was lower in our analysis. It may be due to two children included (age 8 and 10). When these children were excluded mean age was found 38 $\pm$ 12 years (16-63 years). Our patient was 38 years old, similar to the age of other cases in the literature.

Figure 1. Ultrasonography shows the absence of the isthmus and the left thyroid lobe. Heterogeneous parenchymal echogenicity is apparent in the right thyroid lobe.

Figure 2. Thyroid scan with 99m-technetium showed homogeneous uptake of the radioisotope only in the right lobe.

Nb.	Year	Author (ref. no)	Age/ gender	Initial presentation	Diagnostic method	Additional features	Ophthalmopathy	Absent site	Presence of isthmus/pyramidal lobe	Treatment	Pathologic diagnosis
1	1971	Charkes (29)	-/F	Thyrototoxicosis	¹²³ I scintiscan and uptake, T3 suppression test, TSH-ST	-	+	L	-/+	ND	-
2-6	1972	Harada (8)	28/F	ND	24 hr ¹³¹ I uptake, ¹³¹ I scintiscan	-	+	L	-/+	Surgery	Struma papillaris
			39/F	ND	24 hr ¹³¹ I uptake, scintiscan with TSH-ST	-	-	L	-/-	Surgery	Struma papillaris
			21/F	Thyrototoxicosis	Basal metabolism test, PBI, ¹³¹ I-T3 resin uptake, 24 hr ¹³¹ I uptake and scintiscan	-	+	L	+/+	MMI+ surgery	Struma basedowificata
			28/F	ND	24 hr ¹³¹ I uptake	-	+	R	-/-	Surgery	Struma basedowificata
			58/F	ND	24 hr ¹³¹ I uptake, scintiscan with TSH-ST, T3 resin uptake, ¹³¹ I-scintiscan and uptake, T3 suppression test, TSH-ST	-	+	L	+/-	Surgery	Struma papillaris
7-9*	1973	Jaffiol (30)	53/M	ND	¹³¹ I-scintiscan and uptake, T3 suppression test, TSH-ST	-	+	R	-/-	ND	-
			28/F	ND	¹³¹ I-scintiscan and uptake, T3 suppression test, TSH-ST	-	+	R	-/-	ND	-
			40/F	ND	¹³¹ I-scintiscan and uptake, T3 suppression test, TSH-ST	-	-	L	+/-	ND	-
10	1975	Burman (2)	41/F	Thyrototoxicosis	T3 resin uptake, 24 hr ¹³¹ I uptake, ^{99m} Tc-scintiscan, TSH-ST	-	-	L	+/-	3 mCi RAI	-
11,12*	1976	Hartemann (31)	58/F	ND	¹³¹ I-scintiscan and uptake, TSH-ST	-	ND	L	-/-	ND	-
			55/F	ND	¹³¹ I-scintiscan and uptake, T3 suppression test, TSH-ST	-	+	L	-/-	ND	-
13,14*	1979	Letonturier (32)	30/F	ND	^{99m} Tc-scintiscan	-	ND	R	ND	ND	-
			23/F	ND	¹³¹ I-scintiscan and uptake	-	ND	R	ND	ND	-
15	1979	Friedman (33)	52/M	Thyrototoxicosis	24 hr ¹³¹ I uptake	-	ND	L	+/-	PTU and 4.8 mCi RAI	-
16*	1980	Mariani(34)	28/F	ND	¹³¹ I-scintiscan and uptake, TSH-ST	-	ND	R	ND	ND	-
17	1981	Mortimer (35)	20/F	Thyrototoxicosis	24 hr ¹³¹ I uptake, LATS/LATS-P stimulation test, anti-TPO, anti hTG	The first use of antibody	+	L	-/-	Surgery	Diffuse toxic hyperplasia
18	1982	Matsumura (15)	35/F	Thyrototoxicosis	T3 resin uptake, 24 hr ¹³¹ I uptake, scintiscan with TSH-ST, TRH stimulation test, TBG, T3 suppression test	First case of T3 thyrotoxicosis	-	L	-/-	MMI	-
19*	1987	Ban (27)	30/M	ND	¹³¹ I-scintiscan and uptake, ^{99m} Tc-scan, T3 suppression test, TRH test, CT	-	+	L	+/-	ND	-
20	1991	Sasaki (36)	28/F	Thyrototoxicosis	¹²³ I uptake, ^{99m} Tc-scintiscan, anti-mitochondrial antibody, anti-hTG, TBII, TSAb, US, CT, MR,	The first use of CT and MRI	-	R	-/-	MMI	-
21,22	1992	Shechner (23)	33/F	Thyrototoxicosis	TSL, TSH-ST, ^{99m} Tc-scintiscan	-	-	R	-/-	PTU and 12 mCi RAI after relapse	-
			35/F	Thyrototoxicosis	TSL, ^{99m} Tc-scintiscan, TSH-ST	-	-	L	-/-	PTU	-
23-25	1994	Ozaki (9)	43/F	Goiter	T3 resin uptake, Basal metabolism test, protein bounding iodine, ¹³¹ I-uptake, TSH-ST, scintiscan	-	-	L	+/-	Surgery	Struma basedowificata
			16/F	Goiter	24 hr ¹³¹ I scintiscan and uptake	-	-	L	-/+	Surgery	Struma basedowificata
			47/F	Goiter	24 hr ¹³¹ I uptake, TRAb, US	-	+	R	-/+	Surgery	Struma parenchymatosa
26,27	1995	McHenry (11)	17/M	Thyrototoxicosis and goiter	Scintiscan	Incidental finding during operation	ND	L	+/-	Surgery	GID and autoimmune thyroiditis

	31/M	Thyrototoxicosis	Scintiscan	-	ND	L	+/-	Surgery	GD
28	1999	Bando (16)	40/F	Hypothyroidism	Anti-TPO, TBII, TSAb, TSBAb, ^{99m} Tc-scintiscan, US, FNAB	R	-/-	MMI and LT4	-
29	1999	Mikosch (37)	57/F	Thyrototoxicosis	^{99m} Tc-scintiscan, TRAb., anti-TPO, anti-hTG, US	L	-/-	Thiomazole	-
30	2000	Veliz (38)	35/F	Thyrototoxicosis and goiter	¹³¹ I-uptake, TRAb, anti-TPO, anti-hTG, ^{99m} Tc-scintiscan, US	L	-/-	PTU	-
31	2001	Zangenh (39)	31/F	Thyrototoxicosis and goiter	US, 24 hr ¹³¹ I uptake, ^{99m} Tc-scintiscan, TSIG	L	+/-	ND	-
32	2001	Hervás-Benito (40)	45/F	Thyrototoxicosis	^{99m} Tc-scintiscan, US, TRAb	R	-/-	ND	-
33	2003	Lee (18)	44/F	Thyrototoxicosis	¹³¹ I-scintiscan, 24 hr RAI uptake, anti-TPO, anti-hTG, US	L	+/-	ND	-
34	2004	Özgen (41)	29/F	Thyrototoxicosis and goiter	Anti-TPO, anti-hTG, ^{99m} Tc-scintiscan, US, TRAb	L	-/-	PTU	-
35	2005	Baldini (19)	41/F	Thyrototoxicosis and goiter	Anti-TPO, ^{99m} Tc-scintiscan, US, TRAb	L	+/+	MMI	-
36	2005	Zakir (42)	22/F	Thyrototoxicosis	US, ^{99m} Tc-scintiscan, second scintiscan.after 24 hrs	L	+/-	ND	-
37	2008	Ruchala (17)	49/F	Hypothyroidism	Anti-TPO, anti-hTG, Tc -99m scintiscan, US, TRAb, 24 hr ¹³¹ I uptake	L	+/-	Thiomazole and 5 mCi RAI	-
38	2009	Nebesio (20)	10/F	Thyrototoxicosis	^{99m} Tc-scintiscan, US, TRAb	L	+/-	19.52 mCi RAI	-
39	2009	Cakir (21)	55/F	Thyrototoxicosis	Anti-TPO, anti-hTG, ^{99m} Tc-scintiscan, US, TRAb	L	-/-	Surgery	ND
40	2009	Serdengecti (43)	8/F	Thyrototoxicosis	Anti-TPO, anti-hTG, ^{99m} Tc-scintiscan, US, TRAb, TSIIg	L	+/-	ND	-
41	2009	Kebapcilar (22)	43/F	Thyrototoxicosis	Anti-TPO, anti-hTG, ^{99m} Tc-scintiscan, US, TRAb	L	+/-	PTU	-
42	2010	Berker (44)	63/M	ND	Anti-TPO, anti-hTG, ^{99m} Tc-scintiscan, US, TRAb	L	-/-	PTU	-
43	2014	Philip (45)	50/F	Goiter	Anti-TPO, US, ^{99m} Tc-scintiscan and uptake	R	-/-	ND	-
44	2015	Present case	45/F	Thyrototoxicosis	Anti-TPO, anti-hTG, Tc-99m scintiscan and uptake, US, TRAb	L	-/-	MMI	No surgery

* Review by Ozaki from Table 2.

ND: No data, F: Female, M: Male, L: Left, R: Right, GD: Graves' disease, US: Thyroid ultrasonography, MMI: Methimazole, PTU: Propylthiouracil, TRAb: TSH receptor antibody, CT: Computed tomography, MRI: Magnetic resonance imaging, I: Iodine, TSH: Thyroid - stimulating hormone, hr: hours, anti TPO: Thyroid peroxidase antibodies, anti-hTG: Thyroglobulin antibodies, TRH: Thyrotropin releasing hormone, TSH-ST: TSH stimulation test, TSI: thyroid stimulating immunoglobulin, ^{99m}Tc: Technetium 99m-Pertechnetate, TBG: Thyroid binding globulin, TBII: TSH-binding inhibitor immunoglobulin, TSBAb: TSH-Stimulation Blocking Antibody, TSAb: Thyroid Stimulating Antibody, LATs: Long-acting thyroid stimulator, LATs-P: Long-acting thyroid stimulator, protector, PBI: protein-bound iodine, FNAB: Fine needle aspiration biopsy.

According to the literature TH is more common in females with a female-to-male ratio of 3:1 (1, 13). GD is not an exception (female-to-male ratio is 5:1) to with a female-to-male ratio of 6.3:1. This ratio reflects gender ratio of GD instead of TH. It may be due to the fact that diagnosis of TH is delayed until hyperthyroidism related complaints occur.

In our analysis left side was absent in 33 (75%) cases and right side in 11 (25%). Left lobe is absent in the majority of thyroid hemiagenesis. According to the review by Mikosh *et al.* the ratio of absent side was 3.6:1 (left:right) in 256 cases analysed (absent side was reported in 224 cases) and isthmus was present in 44% (13). The ratio is similar in association of thyroid hemiagenesis and GD. We found the left-to-right ratio as 3:1 in our analysis. Isthmus was present in 17 (39%) cases and was absent in 24 (55%). Data about isthmus was missing in 3 cases. Left lobe and isthmus were absent in our patient similar to the literature.

Symptoms and findings of GD are similar to those of other types of thyrotoxicosis. But extrathyroidal manifestations of GD such as orbital disease, skin changes and fingertip and nail abnormalities are unique. Only about 30–50% of patients have clinically apparent orbitopathy (14). Orbital status of 34 out of 44 patients analysed were documented. Sixteen (36.4%) had Graves orbitopathy related findings. Orbitopathy was not detected in our patient, this finding was similar to that reported in the literature.

Some of the reported cases of TH in 70s and 80s had association with GD. Cases reported after 90s had significant association with GD. A case of T3 thyrotoxicosis associated with TH was reported in 1982 (15). In following years 2 cases of TH developing GD after hypothyroidism (16, 17), one familial form (18), one nodular variant GD developing spontaneous hypothyroidism after following medical treatment (19), one case of Down syndrome developing GD following hypothyroidism (20), one multinodular goiter (21) and one hypercalcemia associated with GD (22) were reported.

TSH stimulation test and scintiscan with Tc-99 or Iodine had been used until 1990s for differential diagnosis of GD and TH. Thyroid autoantibodies were used afterwards and TSH stimulation test was abandoned. Shechner C. *et al.* indicated thyroid-stimulating immunoglobulin (TSI) was more efficacious for distinguishing GD from toxic adenoma and TSH stimulation test was obsolete in 1992 (23). TRAb measurement was first reported in a case report in 1994 (9).

In a patient with suspected hyperthyroidism, it is advised to measure serum free T4, free T3 (or total T3) and TSH levels first to evaluate thyroid status (24). The second step in diagnosis of hyperthyroidism is RAI uptake and thyroid scintiscan or if unavailable or contraindicated measurement of TRAb according to the ATA and AACE guidelines published in 2011 (25). Serum TRAb measurement is an efficacious test to differentiate GD from other causes of hyperthyroidism. AntiTPO which is positive in another autoimmune disease, Hashimoto thyroiditis, can also be detectable in GD. TRAb measurement by modern immunoassay and bioassay has high specificity and sensitivity. Therefore it is of value in differential diagnosis of hyperthyroidism (26). The same proposition would be valid for association of TH and GD.

Thyroid US is a noninvasive, inexpensive, and sensitive mode of imaging and it can be used in diagnosis of GD as well as in nodular thyroid disease. Before 1991, there was no information about whether US was performed or not in the analysed cases, After 1991 almost all case reports yielded US data and some published imaging prints. In addition computed tomography (CT) and magnetic resonance imaging (MRI) are also useful to distinguish between unilateral thyroid disease and true TH (27).

Differential diagnosis of all possible hyperthyroidism causes including toxic adenoma and toxic multinodular goiter should be made in the presence of nodule or goiter without ocular findings supporting GD. Unilateral radioactive substance uptake can be confused with toxic nodule. Suppressed lobe becoming visible after TSH stimulation excludes TH and diagnosis of solitary hyperfunctioning nodule is confirmed with triiodothyronine suppression test (2). Scintiscan with Tc-99m MIBI can be used as an alternative and more practical method to demonstrate suppressed thyroid tissue (28). Acute and chronic unilateral inflammatory diseases, primary neoplasms, metastasis of malignancies, and infiltrative diseases like amyloidosis should also be kept in mind.

TH is a rare inborn anomaly occurring if one of the thyroid lobes fails to develop. During embryologic development the thyroid gland forms as a diverticulum on the floor of primitive pharynx. As the downgrowth of thyroid diverticulum proceeds, the canal between tongue and thyroid diverticulum forms thyroglossal ductus. During descent, the diverticulum forms two lobes. When thyroid reaches the final position, thyroglossal ductus vanishes. Disturbance in lobulation and descent due to unknown etiology leads to ectopic

sublingual thyroid and thyroglossal duct cyst formation. Although the exact pathology remains unknown, it is suggested that failure of the cells to migrate laterally results in TH. No putative gene has been demonstrated. Therefore thyroid pathologies occurring during embryologic development should also be kept in mind in differential diagnosis of TH.

The aims of treatment for GD are achieving normal thyroid function, avoiding hypothyroidism, and recurrence of hyperthyroidism. There are three treatment modalities including pharmacological treatment, ¹³¹I-RAI therapy and near-total or total thyroidectomy. We reached the information about treatment modalities in 29 out of 44 cases of TH with GD. Twelve cases underwent surgery, 11 cases were treated with antithyroid drugs (thiomazole and its derivatives or PTU), and 6 cases received a dose of 3-19.52 mCi RAI therapy.

In conclusion, majority of TH cases are detected by physical examination or on imaging during work-up of thyroid disease. Asymptomatic cases are detected incidentally or in autopsy series. In 1970s TSH stimulation test was used in diagnosis of TH and T3 suppression test for differential diagnosis of thyrotoxicosis. Less invasive, inexpensive, and easy to perform laboratory tests (autoantibodies) and imaging modalities (US and scintiscan with Tc) replaced these tests. In addition CT, MRI, and FNAB may be helpful in the differential diagnosis. Diagnosis of GD associated TH is not challenging nowadays. But it is of utmost importance to bear this congenital anomaly in mind in order to make differential diagnosis of solitary autonomous adenoma fulfilling the lobe since treatment modalities are different.

Conflict of interest

The authors declare that they have no conflict of interest.

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