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CASE REPORT

Medicine Science International Medical Journal

Medicine Science 2017;6(1):154-6

Two siblings with familial subclinical hyperthyroidism with unknown etiology

Elif Ozsu[1], Gul Yesiltepe Mutlu[2], Filiz Mine Cizmecioglu[3], Rifat Bircan[4], Sukru Hatun[2]

[1]Department of Pediatrics, Samsun Obstetrics and Children Hospital Samsun, Turkey
[2]Koç University, School of Medicine, department of Pediatric Endocrinology İstanbul,Turkey,
[3] Kocaeli University School of Medicine, Department of Pediatric Endocrinology, Kocaeli, Turkey
[4]Namık Kemal University College of Science, Department of Molecular Biology and Genetic Tekirdağ, Turkey

Received 18 August 2016; Accepted 18 October 2016
Available online 26.10.2016 with doi: 10.5455/medscience.2016.05.8537

Abstract

Subclinical hyperthyroidism is defined as low or undetectable concentration of serum thyrotrophin (TSH) with normal free triiodothyronine (FT3) and free thyroxine (FT4) levels. [1)]. Familial subclinical hyperthyroidism is a rare entity. Activating mutations of the TSH receptor (TSH-R) gene cause genetic hyperthyroidism. Here we present a family with more than one affected individual. All family members were investigated for TSH-R mutation. No mutation was detected, while a A459 polymorphism was found in one of the cases and three other siblings. Despite the clinical and biochemical findings suggesting a TSH-R mutation, a reasonable cause could not be detected. Epigenetic and environmental modifiers, including iodine intake, should be considered in families with mutation negative, familial non auto-immune hyperthyroidism (FNAH).

Keywords: Familial, subclinical hyperthyroidism, genetics

Introduction

Subclinical hyperthyroidism is a condition describing the low TSH levels with normal thyroid hormone levels [1-3]. The prevalence of subclinical hyperthyroidism is 0.5% in children and 15% in elderly [4]. The definition is based on laboratory findings. It can be transient or permanent. Although serum thyroid hormones are in the normal reference ranges, they might be high for the individual. Low or undetectable serum TSH levels suggest a mild tissue hyperthyroidism. Heart and bone are the most common affected organs. Although it is rare, TSH-R mutations must be considered when cases are familial and non-autoimmune. TSH-R activating mutation is a rare entity leading to familial hyperthyroidism. Activating mutations in this receptor can cause not only familial non-autoimmune hyperthyroidism and toxic adenoma, but also severe hyperthyroidism requiring surgery in neonatal period [3]. Beside these severe clinical presentations, TSH-R mutations can also be the cause of subclinical hyperthyroidism. In this study it was aimed to present two siblings with subclinical hyperthyroidism. Despite the presence of clinical findings of hyperthyroidism and goiter, no mutation was detected in TSH-R.

***Corresponding Author:** Elif Ozsu, Department of Pediatrics, Samsun Children's and Obstetrics Hospital, 55000/İlkadım, Samsun, Turkey
E-mail: elozdr@gmail.com
Tel: +905054547589

Case-1: An 11-year-old male patient admitted to our clinic with the complaints of a swelling on the anterior neck, palpitation and nervousness. The swelling occurred nearly 5 years ago. He had previously been evaluated by a pediatric cardiologist because of his tachycardia and no pathologic finding had been determined. The patient was born from consanguineous parents, without any complications following the pregnancy and had no health problems. His mother, sister (Case-2), aunt and grandmother were suffering from goiter. The physical examination revealed normal anthropometric measurements and pubertal stage was Tanner Stage-3. The heart rate was 100/min, goiter was a grade-2 and exophthalmos was not observed. Thyroid function tests were indicating subclinical hyperthyroidism. Serum FT3 level was 4.92 pg/ml (N: 2-4), FT4 was 1.23 ng/ml (N:0.8-2.3) and TSH was 0.199 uIU/ml (N: 0.5-4.8). Thyroid auto-antibodies and thyroid receptor anti-body (TRAB) were negative. Thyroid ultrasound imaging revealed a total thyroid volume of 34.73 ml, which is increased for his age. Graves ophthalmopathy was not detected in ophthalmologic assessment. No treatment was given to the patient. In the follow-up period an increase was observed in TSH level of the patient. At the end of one year hormone levels were as follows; TSH: 0.476 uIU/ml, FT4:1.22 ng/ml, FT3:4.75 pg/ml.

Case 2: A 12-year-old female (sister of case 1) was admitted to our clinic with the complaint of nervousness

for two years. Stage-2 goiter was found in physical examination. Goiter was also present in several relatives. Anthropometric measurements were normal and pubertal stage was Tanner Stage-2. The heart rate was 104/min and the blood pressure was 130/70 mmHg which are over the average levels. TSH was 0.3 uIU/ml, FT3 was 4.66 pg/ml and FT4 was 1.45 ng/dl, thyroid auto-antibodies and TRAB were negative. Thyroid volume was 32 ml (N: < 9.2 ml). Ophthalmologic assessments revealed normal ocular findings. No treatment was given either. At the end of one year hormone levels were as follows: TSH: 0.2 uIU/ml, FT3: 4 pg/ml, FT4: 1.27 ng/dl.

Urinary iodine excretion of both patients were normal. Patients were thought to have FNAH, since goiter was present, auto-antibodies were negative and the mother had overt hyperthyroidism. Clinical and laboratory findings of the mother revealed overt hyperthyroidism (TSH: 0.007 Uıu/ml, free T3: 5.10 pg/ml, free T4: 1.74 ng/dl). Thyroid auto-antibodies and TRAB were negative. Radioactive iodine (RAI) ablation was performed, since she did not respond to the medical treatment.

Thyroid function tests (TFT) and autoantibody levels (Anti- Thyroglobuline and Anti Thyroid-peroxidase) of all parents and all siblings were evaluated. DNA samples of the family members were sent to a research center for genetic analyses. A silent A459A mutation was determined in Case-1 and three other siblings (Table 1) but according to the current knowledge this mutation did not lead to receptor autonomy. Eventually, it was interpreted that there was no change in TSH receptor or Gsα sequence in any members of the family. Then, what was the underlying pathology of subclinical hyperthyroidism involving at least three generations? Goitrogenic substance exposure was questioned in the family history, but no exposure was identified.

Table 1. Thyroid function condition and A459A polymorphism of all family members.

	TSH-1 (uIU/ml)	TSH-2 (IU/ml)	Ft4-1 (ng/dl)	Ft3-1 (pg/ml)	Ft4-2 (ng/dl)	Ft3-2 (pg/ml)	Anti-TPO (IU/ml)	Anti-TG (IU/ml)	Polymorphism A459A
Case 1(proband)	0,199	0,486	1,23	4,92	1,22	4,75	negative	Negative	present
Case 2(proband)	0,4	0,2	1,68	4,66	1,2	4,2	negative	Negative	lacking
Sibling1	0,079	0,32	1,41	4,69	0,95	3,34	negative	Negative	lacking
Sibling2	0,114	0,32	1,41	3,94	1,07	3,21	negative	Negative	lacking
Sibling3	0,902	0,94	1,44	4,59	1,09	3,34	67	Negative	present
Sibling4	0,511	0,90	1,36	4,48	1	3,60	negative	Negative	present
Sibling5	1,12	1,12	1,16	4,73	1,09	3,56	negative	Negative	present
Sibling6	0,453	0,51	1,65	4,81	1,19	4,19	negative	Negative	lacking
Mother	0,007	0,193	1,74	5,10	1,13	2,77	negative	Negative	lacking
Father	0,37		1,65	3,54			190	113	lacking

Discussion

We report two siblings with familial non-autoimmune subclinical hyperthyroidism, in whom we were unable to explain the underlying etiology. Although non-autoimmune overt hyperthyroidism is very rare, TSH-R activating mutations as a cause of subclinical hyperthyroidism may be more common and should be considered in the differential diagnosis, especially in familial cases [1-3]. We investigated TSH-R mutation in two siblings because of their subclinical hyperthyroidism and family history. However, we could not find any mutation.

Clinic and laboratory findings may be variable in TSH-R mutations. Some members of the same family, with the same mutation, may have overt hyperthyroidism, while the others have subclinical hyperthyroidism. In addition, some cases might be diagnosed in advanced ages [4,5].

Since the TSH levels of our patients were mildly suppressed (0,12 - 0,4 uIU/ml) and cardiologic findings were normal, treatment was not administered. Even though the patients complained from palpitation and nervousness at referral, these complaints did not persist and their TSH levels increased in the follow-up period. However, TSH level of their mother was severely suppressed and we learned that RAI therapy was applied since she did not respond to antithyroid treatment. Could mother's unresponsiveness to treatment be the indicator of receptor mutation? However, no mutation was found in mother either. FNAH cases must also be kept in mind that they can become complicated with autoimmune thyroid illness, which is supported by some case reports in the literature. In 25% of these cases, who even do not have goiter, lymphocytic infiltration could be observed by light microscopy in the biopsy material [3,6].

Analysis of genotype–phenotype correlations in non-autoimmune hyperthyroidism exposed no consistent relationship between in vitro activity of the mutant TSH-R and the clinical course of the disease [4]. This suggests that other genetic, epigenetic, and environmental modifiers, including iodine intake, might also affect the clinical features. Some individuals with the same germline TSHR mutation,in the same family they can show different clinical findings at different age. It can be explained by dietary iodine intake

Some people in the normal population have a mild depression in the TSH level, which might be caused by a polymorphism in TSH-R sequences. These patients are generally the ones whose thyroid stimulating antibodies are negative and the clinical findings of hyperthyroidism are occurring at an advanced age. The hypothesis that a population of normal people with relatively low TSH level would correspond to defined genetic polymorphisms in TSH-R sequences. It can also be checked for the possibility of mild FNAH in elder patients who have hyperthyroidism with negative TRAB [5].

TSH-R polymorphism was identified in Case-1 and other three siblings and it is known that this alteration does not lead to receptor autonomy. Acute suppurative thyroiditis and transient hyperthyroidism should be considered in the differential diagnosis [6,7]. Could hyperthyroidism be due to the inflammatory period of an acute or sub-acute thyroiditis? This was excluded with negative inflammation criteria and normal sedimentation levels. Some medicine, such as sibutramine, lithium and interferon-alpha, may also cause hyperthyroidism. However, our patients were not receiving any kind of medication [8-10].

Environmental factors also lead to these kind of thyroid problems with a quite wide presentation. Symptoms may emerge as mild and even late onset in individuals living in iodine-poor regions and having iodine deficiency. Urinary iodine levels in our two patients were normal. Patients can also admit to hospital in 5th or 6th decade with mild findings. These cases may even present with a cold thyroid nodule. As soon as toxic nodular goiter is excluded, this condition must be considered. Sometimes these cases can also be misdiagnosed with Graves disease. Patients with hyperthyroidism, even if it is a subclinical hyperthyroidism, are under the risk of having bone health problems and heart failure. So, treating these cases, particularly the ones with a TSH level of below 0.1 uIU/ml, is recommended [6,11]. Although urinary iodine levels were normal at the time of diagnosis, the presence of subclinical hyperthyroidism in four siblings with no detected mutation made us think that there was a peripheral exposure.

Acknowledgements: The authors would like to thank all patients and their family

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