Pediatric Endocrinology Diabetes and Metabolism
Endokrynologia, Diabetologia i Choroby Przemiany Materii Wieku Rozwojowego

Case Report | Praca kazuistyczna
Pediatr Endocrinol Diabetes Metab 2016;22,2:76-79
DOI: 10.18544/PEDM-22.02.0055

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Graves' disease in 2.5 years old girl – 6-year-long observation

Choroba Gravesa u 2,5 letniej pacjentki – 6-letnia obserwacja

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Abstract

Introduction. Pediatric Graves' disease is rare in young children, more frequent in children with other autoimmune diseases or with family history of autoimmune thyroid disease. **Case report.** The 2.5 year old girl was admitted to the hospital with tachycardia and subfebrile temperature. The girl presented symptoms of atopic dermatitis. Child's mother was diagnosed with Hashimoto disease two months after the child's diagnosis. In physical examination of the child, enlarged thyroid was found. At the admission, the laboratory tests revealed decreased TSH (0.001 uIU/ml), increased both FT3 (>30 pg/ml) and FT4 (3.43 ng/dl), but normal levels of anti-thyreoglobulin antibodies (ATG – 0.64 IU/ml) and anti-thyroid peroxidase antibodies (ATPO – 0 IU/ml); thyrotropin receptor antibodies (TRAb) were not identified. The Graves' disease was diagnosed. The girl started treatment with methimazole (2x5mg) and propranolol (due to tachycardia, 2x5mg). The thyroid function (TSH, FT4 and FT3) normalized 1 year after diagnosis and hormone levels remained within normal reference values, but she received methimazole for 18 months. At presen, the patient is 8 years old. She is not receiving any treatment and her thyroid function is correct. The girl still presents symptoms of atopy. **Conclusion.** In case of symptoms of tachycardia in children, the hyperthyroidism should be taken into consideration. Numerous methods of treatment provide a therapy appropriate to the age and condition of patients. Long remission after treatment with antithyroid drugs could also be achieved in younger (prepubertal) children.

Key words:
Graves' disease, children, thyreostatics

Streszczenie

Wstęp. Dziecięca postać choroby Gravesa występuje rzadko u małych pacjentów, częściej u dzieci z chorobami autoimmunologicznymi albo z rodzinnym występowaniem chorób autoimmunologicznych. **Opis przypadku.** 2,5-letnia dziewczynka została przyjęta do szpitala z tachykardią i stanem podgorączkowym. W wywiadzie: atopowe zapalenie skóry u dziecka, choroba Hashimoto u matki (zdiagnozowana 2 miesiące po postawieniu diagnozy u dziecka). W badaniu fizykalnym zaobserwowano powiększony gruczoł tarczowy. W badaniach laboratoryjnych przy przyjęciu stwierdzono nieprawidłowości wskazujące na nadczynność tarczycy: TSH – 0,001 uIU/ml, FT3 >30 pg/ml, FT4 3,43 ng/dl oraz prawidłowy poziom przeciwciał ATG i ATPO. Rozpoznano chorobę Gravesa i rozpoczęto leczenie metimazolem (2x5 mg) oraz propranololem (ze względu na tachykardię 2x5 mg). Po rocznym leczeniu uzyskano stabilizację funkcji tarczycy, jakkolwiek pacjentka otrzymywała leczenie metimazolem przez 18 miesięcy. Obecnie pacjentka ma 8 lat i nie otrzymuje żadnego leczenia, funkcja tarczycy pozostaje prawidłowa, natomiast wciąż prezentuje objawy atopii. **Podsumowanie.** Przy występowaniu tachykardii u małego dziecka należy rozważyć rozpoznanie nadczynności tarczycy. Wybór terapii powinien zależeć od wieku i stanu dziecka. Długotrwała remisja nadczynności tarczycy niewymagająca leczenia jest również możliwa u młodszych (przed okresem dojrzewania) dzieci.

Słowa kluczowe:
choroba Gravesa, dzieci, tyreostatyki

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Received: 05.06.2016.
Accepted: 20.01.2017.
Conflict of interests: none declared.

Pediatr Endocrinol Diabetes Metab 2016;22,2:76-79

Introduction

Normal thyroid function is important for proper childhood development. Hypothyroidism occurs in young children more often than hyperthyroidism. The most common cause of thyrotoxicosis in children is Graves' disease (GD). GD is an autoimmune disorder where the thyroid is stimulated to produce excess hormones by TSH receptor antibodies (TRAb). The incidence of GD in children is about 1:10,000 [1]. Graves' disease is more frequent in children with other autoimmune diseases or family history of an autoimmune thyroid disease [2]. It occurs more often in girls than in boys, although no gender differences are noted in children under 4 years old [3]. The following signs andsymptoms of hyperthyroidism may be observed: goiter, tachycardia, hypertension, exophthalmos, weight loss, acceleration of linear growth, irritability, impaired concentration, and heat intolerance. A child with persistent tachycardia should be evaluated for hyperthyroidism.

Case report

A female 2.5 years old patient, born from the first pregnancy, was admitted to the hospital with tachycardia and subfebrile temperature. Two weeks before the submission the child had the upper respiratory tract infection with lymphadenopathy and hepatosplenomegaly. She received amoxicillin with clavulanic acid, followed by rash and swelling of the eyelids.

According to her medical history, the child suffers from atopic dermatitis and food allergy. There was family history of autoimmune thyroid disease; child's mother was diagnosed with Hashimoto disease two months after the diagnosis of the child. Pregnancy, perinatal and development during infancy were undisturbed.

At the admission, the general condition of the patient was good; there were no visible signs of infection or dehydration. Anthropometric parameters were assessed (height 99 cm – 97 percentile, weight 14.8 kg – 25 percentile). The skin was damp, atopic. Peripheral lymph nodes were palpable, thyroid palpated was slightly enlarged. Heart rate was regular, 150/min, temperature 37°C. The liver was enlarged (1cm under the costal margin), no splenomegaly was observed.

Laboratory studies have demonstrated anemia, thrombocytosis, lymphocyte blood smear, and slightly elevated kinase keratin. No additional parameters of inflammation or abnormalities at the level of liver enzymes were found. In the chest, X-ray cardiac silhouette was not enlarged.

Due to the tachycardia, Holter monitor examination was performed – there was normal sinus rhythm with a frequency of 155/min. Because of the abnormalities of the thyroid hormones, the patient was transferred to the department of endocrinology, where diagnostics on the thyroid gland was performed.

The girl was in hyperthyreosis. The laboratory tests revealed: decreased TSH – 0.001 uIU/ml (norm 0.490–4.670 uIU/ml), elevated both FT3 – >30 pg/ml (norm 1.45–3.5 pg/ml) and FT4 – 3.43 ng/dl (norm 0.7–1.9 ng/dl), increased levels of thyroglobulin – 256.7 ng/ml (norm 0.2–70.0 ng/ml), normal values of ATG – 0.64 IU/ml (norm 0.1-34 IU/ml), and the absence of ATPO (0 IU/ml). At the time of the diagnosis the level of TRAb was not evaluated. Ultrasonography revealed enlarged thyroid, reduced echogenicity without focal lesions, with increased vascular flow in both lobes. The scintigraphy showed an increased binding of technetium (22%). On the basis of these studies the patient was diagnosed with Graves' disease. The girl started treatment with methimazole (2x5 mg) and propranolol (2x5 mg). After 10 days of treatment, control examination was performed, where the normalization of hormone levels was found. The girl was discharged from the hospital in good condition. After 4 months of therapy,due to episodes of hypothyroidism, levothyroxine was included to the treatment..

The thyroid function (TSH, FT4 and FT3) and blood morphology were monitored on a monthly basis to control the progression of the disease and determine the appropriate doses of medications. The results of the parameters of thyroid function (TSH, FT4, FT3), thyroid antibodies (ATG, ATPO, TRAb), in Table I.

The laboratory tests performed throughout the observation period revealed: thrombocytopenia, decreased levels of erythrocytes, and increased levels of macrophages. The first evaluation of the level of TRAb (17.75 IU/ml) was performed when the girl was 3 years old (7 months after the diagnosis). At that time she was in subclinical hyperthyreosis (decreased TSH 0.015 mIU/ml, normal FT4 0.9 pg/ml). Then, antibodies against the TSH receptor (TRAb) systematically decreased to the normal range, and normalized (TRAb 1.14 IU/ml) when the child was 4.5 years old (after 2 years of observation). ATPO remained within normal limits. Episodes of hypothyroidism and hyperthyroidism were observed for more than a year after the diagnosis of Graves' disease.13 months after the diagnosis hormone levels normalized (TSH 0.737 mIU/ml, FT4 1.23 pg/dl) and remained within normal ranges during further observation. The child ended the therapy of methimazole following18 months of treatment.

At present, the patient is 8 years old. She is not receiving any medicaments. Thyroid function is normal (TSH 1.42 mIU/ml, FT4 16.1 pmol/l). Antibody levels are within the normal ranges (ATG 55.6 IU/ml, ATPO 8.13 IU/ml, TRAb 0.79 IU/ml).

The girl does not present evidence of any developmental disorders, but still shows the symptoms of atopy. Due to the symptoms of allergy, the dairy products and gluten are reduced in her diet.

Discussion

Graves' disease is the most common cause of hyperthyroidism both in children and adults, but it is extremely rare in young children [1,4]. There are several reports about Graves' disease in children younger than 4 years old [5,6]. We did not find reports of long observation of the children younger than 4 years old with Graves' disease. We report 6 yearlong, continuous observation of the child with Graves' disease. Family

Table I. Evaluated parameters of thyroid function and thyroid antibodies during observation
Tabela I. *Oceniane parametry funkcji tarczycy i przeciwciała tarczycowe podczas obserwacji*

Age (years and months) Wiek (lata i miesiące)	FT3 pg/ml (normal range)	FT4 ng/dl (normal range)	TSH μIU/ml (normal range)	ATG IU/ml (normal range)	ATPO IU/ml (normal range)	TRAB IU/ml (normal range)
2 years 5 months	>30[1] (1.45–3.5)[2]	2.95 (0.7–1.9)	0.0011 (0.49–4.67)	0.64 (0.1–34)	0 (0.1–12)	-
2 years 6 months	6.52 (1.45–3.5)	1.86 (0.7–1.9)	0.01 (0.49–4.67)	-	-	-
2 years 11 months	5.34 (2.3–4.2)	1.17 (0.89–1.76)	0.008 (0.64–6.27)	-	-	-
3 years	3.52 (2.3–4.2)	0.66 (0.89–1.76)	18.23 (0.64–6.27)	-	-	-
3 years 2 months	4.44 (1.45–3.48)	0.9 (0.8–1.7)	0.015 (0.4–6.0)	16.8 (0.1–34)	8.6 (0.1–12)	17.75 (<1.22)
3 years 5 months	7.08 (2.3–4.2)	1.64 (0.89–1.76)	7.58 (0.64–6.27)	-	-	-
3 years 7 months	3.77 (2.3–4.2)	1.01 (0.89–1.76)	0.54 (0.64–6.27)	-	-	-
3 years 9 months	4.43 (2.3–4.2)	1.36 (0.89–1.76)	0.145 (0.64–6.27)	-	-	-
3 years 11 months	3.98 (2.3–4.2)	1.07 (0.89–1.76)	1.147 (0.64–6.27)	-	-	-
4 years 7 months	4.18 (2.3–4.2)	1.45 (0.89–1.76)	0.606 (0.64–6.27)	<15 (<60)	40.1 (<60)	1.14 (<1.22)
5 years 3 months	4.8 (2.3–4.2)	1.18 (0.89–1.76)	1.058 (0.64–6.27)	<15 (<60)	38.6 (<60)	1.01 (<1.22)
5 years 8 months	3.73 (2.3–4.2)	1.29 (0.89–1.76)	0.726 (0.85–6.5)	26.8 (<115)	8.3 (<34)	0.76 (<1.5)
6 years 2 months	3.97 (2.3–4.2)	1.36 (0.89–1.76)	0.294 (0.28–4.3)	227.5 (<115)	<5 (<34)	0.79 (<1.5)
6 years 5 months	-	1.43 (0.89–1.76)	0.753 (0.28–4.3)	285.2 (<115)	<5 (<34)	-
7 years 7 months	-	1.25 (0.89–1.76)	1.420 (0.28–4.3)	55.6 (<115)	8.13 (<34)	-

history of autoimmune diseases and suffering from other autoimmune diseases are risk factors for developing Grave's disease. In our case, the mother of the child was diagnosed with Hashimoto disease two months after the diagnosis of the child. Furthermore, the child suffers from atopic dermatitis. Most of the patients had classic symptoms and signs of thyrotoxicosis [1]. Ophthalmic abnormalities are less severe in children than in adults, and occur approximately in 25-60% of children [3,4]. Furthermore, Grave's ophthalmopathy occurs less often in children under 10 years old [7]. In our case, the only symptom of hyperthyroidism was tachycardia for amonth. She had no signs of exophthalmos.

The treatment of Graves' disease in children depends on age, thyroid size, the severity of the disease, patient preference, and the availability of methods [2]. Antithyroid drugs are usually used to treat hyperthyroidism, but sometimes surgery or radioiodine therapy are applied [8].

Regardless of age, methimazol is the drug-of-choice in the treatment of Graves' disease because of good tolerability and the possibility of long-term use. This drug is administered in doses of 0.2 to 0.5 mg/kg per day [8]. The best results are achieved by giving the drug in a single dose [5,8]. During treatment, liver enzymes tests and blood tests should be performed because of the risk of agranulocytosis. The other side effects of methimazol include: rash, arthralgia and vasculitis, which are dose-dependent [9]. Therefore, in the treatment of persistent symptoms of hyperthyroidism one should not increase the dose but use beta-blockers [5].

The fT4 and fT3 level tests should be performed every 1–2 weeks until the normalization of hormone levels to evaluate the effectiveness of the treatment [8]. The response to the treatment is not immediate and the normalization of thyroid function can range from several months to several years. However, not all patients achieve the normalization of thyroid function; moreover,

relapse can also occur [2]. The effectiveness is lower in patients with high levels of TRAb and a large volume of thyroid gland at diagnosis [8]. Propylthiouracil is contraindicated in children due to side effects, but it can be used before the radioiodine therapy or surgery, when methimazole is poorly tolerated or in the first 3 months of pregnancy [8,10].

Radioactive iodine is the method recommended for patients over the age of 10, in cases in which the drug treatment is ineffective or associated with severe complications [2,10]. There are reports of the use of radioiodine in the group of young children (<5 years); however, this method is not recommended in this age group [8, 11]. Typical dose is from 100 to 400 Ci/g of thyroid tissue [2, 8]. Efficiency depends on the size of the thyroid gland and is lower when thyroid mass is greater. When the glands is larger than 80 gm, surgery is indicated [8]. The treatment is associated with a small number of complications - mild tenderness over the thyroid (15%) and worsening ophthalmopathy (3%) [8]. There is no risk of genetic mutations, thyroid cancer and other cancers [8]. Hypothyroidism develops about 2-3 months after application of ^{131}I. Then, it is necessary to start substitution levothyroxine.

Surgical treatment is indicated when there are no other treatment options, current treatment is ineffective, methimazole and radioactive iodine are contraindicated, thyroid volume is >80 gm, or there is a relapse [10]. The procedure is difficult and must be carried out by a pediatric surgeon experienced in child-thyroidectomy. Depending on the surgeon's skill, the risk of complications ranges from 4% to 15%. The most common complications include: hemorrhage, recurrent laryngeal nerve paresis, and hypocalcemia associated with parathyroidectomy [2,8]. The levothyroxine therapy should be started on the same day as the surgery [2].

Regardless of the method, all patients require long-term control, consisting of ultrasound of the gland and testing of hormone levels (TSH,fT4) and thyroid antibodies [2,8].

The long term remission after treatment with antithyroid drugs occurs less often in children than in adults. Only 30% of the children treated with methimazole achieve remission lasting at least two years [2]. The remission rate is even lower in prepubertal children (17%) [3]. Most of the children (75%) relapse within 6 months after the end of the treatment with antithyroid drugs [2]. In our case the patient was treated with methimazole. Her thyroid function normalized 13 months after the diagnosis and, since then, the child hasremained in euthyreosis. Now the girl is 8 years old, and does not receive any medicaments. There are no pathological symptoms of thyroid gland; she showed no signs of relapse for at least 4 years. It can be related to undetectable TRAb antibodies, however, they do not exclude thyroid disorders in the future.

In conclusion, in case of the symptoms of tachycardia in children, the hyperthyroidism should be taken into consideration. Numerous methods of treatment provide a therapy appropriate to the age and condition of patients. Long-term remission after the treatment with antithyroid drugs could also be achieved in younger (prepubertal) children.

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