

СТУДИЈА НА СЛУЧАЈ

АВТОИМУН ТИРОИДИТ ПО ДОЛГА УПОТРЕБА НА АГОНИСТ НА ГОНАДОТРОПИН-ОСЛОБОДУВАЧКИ ХОРМОН КАКО ТРЕТМАН ЗА ПРЕДВРЕМЕН ЦЕНТРАЛЕН ПУБЕРТЕТ – ПРИКАЗ НА СЛУЧАЈ

Маја Танкоска¹, Авди Муртезани¹, Констандина Кузевска – Манева², Марина Крстевска-Константинова¹

¹ Оддел за ендокринологија и генетика, Универзитетска клиника за дејски болести, Универзитет „Св. Кирил и Методиј“, Скопје, Република Северна Македонија

² Оддел за кардиологија и ревматологија, Универзитетска клиника за дејски болести, Универзитет „Св. Кирил и Методиј“, Скопје, Република Северна Македонија

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***Кореспонденција:** Марина Крстевска-Константинова Танкоска. Оддел за ендокринологија и генетика, Универзитетска клиника за детски болести, Универзитет „Св. Кирил и Методиј“, Скопје, Република Северна Македонија. E-mail: mkrstevskakonstantinova@yahoo.com

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Печатарски права: © 2020 Марина Крстевска-Константинова - Оваа статија е со отворен пристап дистрибуирана под условите на нелицензирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираат оригиналниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Постојат мал број студии кои пријавиле нарушувања на ендокрината функција по долга употреба на агонист на гонадотропин – ослободувачки хормон (ГнРХа) кај девојчиња. Овој третман е опишан како безбеден и ефикасен од повеќе автори. Прикажуваме случај на невообичаен исход по долготрајна терапија со ГнРХа кај девојче со централен предвремен пубертет (ЦПП) од идиопатска или фамилијарна етиологија. Во период од 4 години, девојчето примало еднаш месечно трипторелин депо. Ние ја испитавме функцијата на тироидната жлезда со мерење на серумските нивоа на тиротропин (ТСХ), тироксин (Т4), тироидни антитела и ултразвук на тироидната жлезда. На 11 години таа развила блага гушавост презентирани како автоимун тироидит, со покачени тироидни антитела и тироидна жлезда типична за Хашимото тироидит. Затоа, предлагаме редовно следење на функцијата на тироидната жлезда кај девојчиња со ЦПП пред и за време на терапија со агонист на ГнРХа.

CASE STUDY

AUTOIMMUNE THYROIDITIS AFTER LONG TERM GONADOTROPIN-RELEASING HORMONE AGONIST TREATMENT FOR CENTRAL PRECOCIOUS PUBERTY: CASE REPORT

Maја Tankoska¹, Avdi Murtezani¹, Konstandina Kuzevska-Maneva², Marina Krstevska – Konstantinova¹

¹ Department of Endocrinology and Genetics, University Pediatric Clinic, Ss. Cyril and Methodius University, Skopje, Republic of North Macedonia;

² Department of Rheumocardiology, University Pediatric Clinic, Ss. Cyril and Methodius University, Skopje, Republic of North Macedonia

Abstract

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Key words: precocious puberty, GnRH treatment, autoimmune thyroiditis

***Correspondence:** Marina Krstevska-Konstantinova M.D. University Clinic of Pediatrics, Medical Faculty, Ss. Cyril and Methodius University. E-mail: mkrstevskakonstantinova@yahoo.com

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There is a small number of studies that have reported abnormalities in endocrine function after a long-term gonadotropin-releasing hormone agonist (GnRH) treatment in girls. This treatment is considered as safe and effective by most authors. We report our second case of unusual outcome of long-term GnRH therapy in a girl with central precocious puberty (CPP) of idiopathic or familial etiology. She has received monthly depot of injections of triptorelin for a time period of 4 years. We have examined thyroid function by measuring serum levels of thyrotropin (TSH), thyroxine (T4), thyroid antibodies and ultrasound of thyroid gland. At the age of 11 years she developed a mild goiter and presented with autoimmune thyroiditis, having elevated thyroid antibodies and ultrasound of thyroid gland typical for Hashimoto thyroiditis. Having in mind these two cases, we suggest a closer monitoring of thyroid function in girls with CPP, before and during therapy with GnRH agonist.

Introduction

Central precocious puberty (CPP) in childhood, of both idiopathic and organic etiologies are often treated with GnRH agonists. This treatment has been considered effective for a long period of time. It has been stated that long treatment in young children with CPP is well tolerated¹. However, we have already reported a case of a girl with CPP who developed autoimmune thyroiditis after a long-term treatment with GnRH agonists². In addition, there were other reports of impaired thyroid functions possibly due to onset of autoimmune thyroiditis³. We report our second case of this possible side effect of treatment.

Case report

A 4.5-year-old girl presented to our Pediatric Endocrinology Department due to premature telarche. Three years later, at the age of 7 years, she was admitted again with complaints of rapid growth of breasts. Pubertal Tanner stage was B3P1A1. Her height was 115.5cm (10th percentile, standard deviation (SD): -1) and weight 22 kg. Based on the height and weight the BMI is 16.5, placing the BMI-for-age at the 81th percentile. The height of the mother was 155 cm and of the father was 165 cm. Her target height was 154 cm. She was born small for gestational age (weight 2500 g, length 43 cm) and during the first year of therapy, she was growing between the 10th and 3rd percentile growth curve. Her family history revealed that several members on the mother's side have had thyroid disease. Her mother had been investigated for CPP, but never treated. The girl did not have dysmorphic features and her karyotype was normal. Bone age was advanced to 8 years and 10 months. Her blood count was normal, as were other laboratory investigations. T4 (thyroxine) was 9.8 ug/dl (normal range 4.6-12 ug/dl) and thyrotropin was 4.9 uIU/ml (0.4-4.0) Thyroid antibodies were negative. Ultrasound of thyroid gland was normal. The standard GnRH

testing showed levels of FSH 3.3 to 11.1 mIU/ml and LH levels 0.16 to 8.5 mIU/ml. Estradiol levels were 70 pg/ml. The ultrasound of ovaries was normal with a normal size for age. The magnetic resonance imaging (MRI) of the brain was normal. She was given continuous GnRHa therapy (triptorelin) 3.75 mg, once a month. She grew at the 3rd percentile growth curve, with adequate suppression of her pubertal development evaluated every month by clinical inspection and every six months for gonadotropin suppression. Due to poor growth and being SGA, growth hormone treatment was proposed, which the parents rejected. At the age of 11 years she developed a mild goiter and presented with autoimmune thyroiditis. T4 was 10.5 ug/dl, TSH 10.5 uIU/ml, thyroid antibodies a-TPO 573 IU/ml (normal range < 60 U/ml); a-TG 2272 U/ml (normal range <60 U/ml), ultrasound of thyroid showed diffuse glandular enlargement with heterogeneous and hypoechoic parenchymal echo pattern, typical for Hashimoto thyroiditis. She was administered levothyroxine 50 micro g/day. Meanwhile the GnRH agonist therapy was discontinued. At the age of 13 years, her puberty was completed, with normal menstrual cycles, but unsatisfactory growth and height of 142 cm (SD: -2). She still attends regular controls for her thyroid status.

Discussion

We report a second case of a girl who developed an autoimmune thyroiditis after treatment with GnRH agonists for idiopathic or familial CPP. Although the period of treatment in this case is shorter (4 years), compared to our previously reported case (8 years), the outcome is similar. Other authors have described an autoimmune thyroiditis in a 9-year-old girl treated with leuprolide acetate⁴.

Amino et al. reported hypothyroidism after treatment with triptorelin⁵ and Miao et al. described three cases of hyperthyroidism³. In a comparative study of group of children, with CPP and

their thyroid outcome after treatment with two different GnRHa, Massart et al. did not find thyroid dysfunction, except for decreased FT3 in both groups. So far, there is no evidence of thyroid dysfunction during GnRHa treatments (leuprolide acetate and triptorelin), and has been concluded that throughout the administration of GnRHa the monitoring of thyroid activity is not required.⁶ Some studies show that after a long term observation, the GnRHa treatment in girls with idiopathic CPP is safe for the mineral density of the bones, the body mass index as well as for the reproductive system, and helpful in reaching adult height close to target height⁷. Beyond everything, we can hypothesize that there can be three possible mechanisms for the hyperthyroidism. The first one is the influence of triptorelin on hyperthyroidism; the second one is the GnRHa triptorelin induced autoimmune thyroid disease (AITD) to destruct the thyroid and the third one is the triptorelin that exacerbates the previously existed AITD⁵.

However, this issue is still controversial, and there has been a lot of debate. In our two cases, it is important to notice that both girls with CPP, treated with GnRH agonists have a family history of thyroid disease.

Some other adverse effects of GnRH agonists have been presented. Sometimes the use of depot form of GnRHa agonists is complicated by sterile abscesses at injection site and anaphylaxis in children⁸⁻¹⁰.

A transient vaginal withdrawal bleeding after the first injection of the agonist has also been reported¹¹⁻¹³. The findings of the study of Yeshaya et al. revealed prolonged and recurrent vaginal bleeding in 8 of 28 patients treated with triptorelin depot.¹⁴ Other studies did not report this phenomenon^{12, 15}. We have observed a transient thrombocytopenia in a girl with CPP (results not published). Further, a study of Warnock et al., where the respondents were women who had endometriosis treated with GnRH agonist, showed an

increase in depressive mood symptoms.¹⁶ In adults too, there is a report of a tricuspid valve thrombus associated with gonadotropin-releasing hormone analogue therapy. It was considered to be related to the procoagulant state induced by hormonal treatment¹⁷. Additionally, another side effect as pituitary apoplexy has been described after administration of leuprolide for carcinoma of the prostate.¹⁸ The previous case that we have described was thought to be a coincidence of a drug treatment, and the presented case shows that other cases of the same pathology appear.

Conclusion

Having in mind our two cases of autoimmune thyroiditis after a long-term therapy with GnRH agonist for CPP in girls, we suggest close monitoring of thyroid function, before and during therapy, especially in patients with a family history of thyroid disease, as well as other autoimmune disease.

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