Case Report

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Does the risk of arterial hypertension increase in the course of triptorelin treatment?

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Abstract

Background: Gonadotropin-releasing hormone agonists (GnRH-a) are common treatment options for central precocious puberty (CPP) in childhood. GnRH-a treatment is useful and has a good safety profile, with minimal adverse effects and no severe long-term consequences. The common side effects in children are menopause-like symptoms and local adverse events at the injection site.

Case presentation: We present the case of a girl with CPP who developed arterial hypertension from treatment with GnRH-a (triptorelin). Comprehensive diagnostic studies ruled out other causes for her hypertension and its complications. After therapy was interrupted, her blood pressure remained within normal limits for age. Consequently, we hypothesize that the hypertension presented by our patient was related to triptorelin treatment.

Conclusions: Although the etiology of this adverse event is not known and only some hypotheses can be made, clinicians should be aware that arterial hypertension might appear during triptorelin treatment in childhood with CPP. Therefore, they should routinely monitor the arterial blood pressure of patients under treatment.

Keywords: arterial hypertension; GnRH-a; precocious puberty.

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Introduction

Precocious puberty (PP) is defined as the onset of secondary sexual development before the age of 8 years in girls and 9 years in boys [1]. The PP is traditionally classified into two categories: central precocious puberty (CPP) and peripheral precocious puberty. Moreover, benign and non-progressive pubertal variants, such as premature adrenarche, premature thelarche, non-progressive or intermittently progressive precocious puberty, are also known. Classically, CPP is more frequent in females [2].

The presence of clinical signs, a bone age higher than chronological age, enlarged ovaries with increased uterine size at pelvic ultrasonography and hormonal data evidencing the activation of hypothalamic-pituitary-gonadal axis are necessary to confirm the diagnosis [2]. In these cases, treatment with gonadotropin-releasing hormone agonists (GnRH-a) may be considered. The therapy has the following primary short-term goals: to suppress the pituitary-gonadal axis and to reduce the development of secondary sex characteristics as well as bone age advancement. Long-term goals are to improve final adult height and to avoid psychosocial or behavioral problems [3, 4].

GnRH-a treatment is useful and has a good safety profile, with minimal adverse effects and no severe long-term consequences [3–5]. Nevertheless, during treatment, patients should be monitored periodically to evaluate pubertal development, height velocity and bone age and to determine how long the treatment should last [3].

Case presentation

A 7-year-old girl presented to our pediatric endocrinology centre with breast enlargement and development of pubic hair, which already lasted for 7 months.

She was born at term by vaginal delivery after an uneventful pregnancy with an appropriate birth weight. The child was breastfed and had regular growth. She had no known allergies, and no noteworthy diseases were reported in the family history. The maternal menarche was reported at 12 years and her target height was 162.5 cm.

At our first clinical examination, the patient appeared in good condition, without dysmorphic features and with normal body proportion. Bodyweight was 35.3 kg (1.13 standard deviations [SD]), height was 135 cm (1.33 SD; 90th percentile) and the body mass index (BMI) was 19 kg/m^2 (0.81 SD). Cardiothoracic, abdominal and genital evaluations were normal. Blood pressure was 105/55 mmHg, within the normal range according to sex, age and height percentile [6]. She showed acne on her back. Her Tanner stage was B3, Ph2.

Pelvic ultrasound showed a longitudinal uterine diameter of 36 mm, whereas bone age was shown to be 2 years higher than her chronological age. Hormonal assays (beta-human chorionic gonadotropin [β-HCG], dehydroepiandrosterone sulfate [DHEAS] Δ4-androstenedione, testosterone, cortisol, thyroid-stimulating hormone [TSH], free thyroxine [FT4]) were normal. A triptorelin stimulation test proved the diagnosis of CPP, evidencing a luteinizing hormone (LH) peak of 26.4 U/L, with an LH/follicle-stimulating hormone (FSH) ratio of 1.22 and an estradiol level of 229 pmol/L. A magnetic resonance imaging (MRI) showed pituitary and central nervous system to be normal.

According to her parents, she began treatment with GnRH-a in a long-acting depot preparation (triptorelin) administered at a dose of 3.75 mg every 28 days. During the therapy, the patient reported only occasional hot flushes and headache. After 6 months, she showed at our endocrinological evaluation a slight reduction in the development of secondary sexual characteristics (Tanner stage: B2, Ph2) and presented a stable BMI (variable between 0.95 and 0.98 SD) and a stable uterine size at pelvic ultrasound (35 mm vs. 36 mm). Her blood pressure remained normal according to sex, age and height percentile.

After 1 year and 6 months from the beginning of the treatment, we found an elevated blood pressure (140/80 mmHg, systolic blood value >99th centile for sex, age and height, diastolic blood value >95th centile for sex, age and height) without other symptoms. These data were confirmed at subsequent controls; we therefore investigated the etiology of this clinical sign.

Blood pressure holter monitoring confirmed hypertension (mean day and night blood pressure values >95th centile for sex, age and height; systolic blood pressure load 62%, diastolic blood pressure load 83%, nocturnal dipping 11.5% [6]). Transthoracic echocardiographic and cardiologist and ocular evaluation were normal and excluded hypertensive complications. Furthermore, renovascular and adrenal diseases were excluded because of normal hormonal assays (urinary steroids, cortisol, aldosterone, active renine, urinary cathecolamine) and normal abdominal ultrasound. Finally, renal vascular Doppler ultrasound was normal with standard velocimetric parameters in both renal arteries. We did not start an antihypertensive treatment, but we suggested a management program, emphasizing appropriate nutrition, with deprivation of salt, and constant physical exercise.

During treatment, her blood pressure values remained elevated in the absence of other symptoms, whereas her pubertal signs were stable. Her parents were very worried about her hypertension and, after other 6 months of treatment, they decided to stop GnRH-a.

After 2–3 months from interruption of therapy, her blood pressure was within the normal limits for sex, age and height. A GnRH test, performed 6 months after the end of treatment, confirmed hypothalamic-pituitary-gonadal axis recovery. Her bodyweight was 48.8 kg (1.19 SD), height was 150 cm (1.20 SD, 90th percentile) BMI was 21.7 kg/m^2 (0.90 SD). Blood pressure holter monitoring was repeated and showed normal values (mean day and night blood pressure values <50th centile sex, age and height [6]; systolic blood pressure load 2%, diastolic blood pressure load 10%, nocturnal dipping 16.1%). Consequently, we can hypothesize that hypertension presented by our patient was related to GnRH-a treatment.

The study was conducted in compliance with the terms of the Helsinki II Declaration. Written informed consent was obtained from the parents of the patient.

Discussion

This brief report underlines the risk of arterial hypertension developing during triptorelin administration for CPP in children who were previously normotensive.

GnRH-a treatment is safe and effective and is generally well tolerated in children and adolescents [3–5]. The depot formulations are effective in maintaining the suppression of pituitary gonadotropin secretion. During the first few weeks after the beginning of the treatment, agonist effects can be observed (“flare-up phase”), but only by the second month of the therapy, significant inhibition is achieved due to desensitization of the pituitary GnRH receptors. Stabilization or regression of clinical signs, such as a decrease in the breast size, decline in the growth rate and uterine size, is observed in all patients. On the contrary, a progression of pubertal signs is indicative of treatment failure [4]. A few days after the initial dose of the GnRH-a was administered, vaginal bleeding may occur due to estradiol withdrawal, because the treatment initially stimulates estradiol production before

suppressing the pituitary gonadal axis. This adverse effect is infrequent and disappears spontaneously, without further treatment. Other infrequent adverse effects are menopausal symptoms, such as headaches, hot flashes or emotional lability, which may occur occasionally, but they are usually short term and do not interfere with the effect of the treatment [4]. Local adverse events like erythema and induration may occur on the site of intramuscular injection [5]. In some cases, these dermatological problems can result in sterile abscesses. Although exceedingly rare, anaphylaxis has been described among the adverse events caused by GnRH-a. Gonadal function is promptly restored in girls after cessation of the treatment, and reproductive potential appears normal in young adulthood. There are conflicting data on the long-term risk of polycystic ovarian syndrome but the therapy does not seem to have any long-term effect on BMI, and a negative impact on bone mineral density. At the moment, no repercussions are known on the timing of menopause and on the health of the offspring [4].

Arterial hypertension is not considered as an adverse event correlated to the use of GnRH-a in children with CPP. Only recently, two reports have described an elevation of blood pressure values in patients treated with GnRH-a [7, 8], but one patient was affected by Williams-Beuren syndrome, that is, a condition associated with an increased risk of hypertension. Nevertheless, the authors ruled out all potential causes of hypertension related to this syndrome and demonstrated a clear association between the GnRH-a therapy and this clinical sign [8]. The other report presented a case that more closely resembled our situation: the patient did not present any predictive factor of arterial hypertension and the timing of the appearance of hypertension was similar. The reported authors explained the origin of hypertension in a healthy girl as the consequence of hypoestrogenism induced by the drug, probably associated with genetic predisposition. They, however, did not consider the role of adiposity [7]. Moreover, in both cases, the severity of hypertension induced the physicians to start an antihypertensive treatment with ramipril and nifedipina in the first case and amlodipine in the second case. On the contrary, in our patient, hypertension was well controlled with dietary measures and physical activity.

Our report confirms the hypothesis that a treatment with GnRH-a may provoke arterial hypertension. In our patient, echocardiography imaging, abdominal ultrasound imaging, renal vascular Doppler and hormonal values were normal, excluding overt cardiovascular and/or renovascular disease, renal parenchymal disease and endocrine causes of hypertension. She presented normal blood pressure before the treatment and she did not have other clinical problems that could cause an increase in the blood pressure levels. Finally, her blood pressure was completely normalized 6 months after the suspension of the treatment. Arterial hypertension was identified after a year and a half of treatment, probably because blood pressure progressively increase over time. Furthermore, considering that the patient was subjected to clinical evaluation only once in 6 months, it is impossible to determine the exact moment when hypertension appeared. Anyhow, in the two previously mentioned reports, the appearance of arterial hypertension was evidenced 3 years and 6 months, respectively, after the beginning of treatment, confirming the slow and progressive onset of this clinical sign.

The cause of this adverse event is not known and only some hypotheses have been put forward. Some authors have speculated that hypoestrogenism induced by GnRH-a treatment may play a role in the elevation of blood pressure levels [7]. Moreover, a hypertensive crisis has been described during triptorelin treatment, and it was attributed to hypoestrogenism [9]. Animal studies have established that a low estrogen level following pharmacological ovariectomy by triptorelin decreases the passive diameter of the small peripheral arteries and venous capacitance function and contractility [10]. These responses may provide the background mechanism for the increased incidence of arterial hypertension and hot flushes during menopause and explain the ability of estrogen substitution to prevent them.

As often signaled, another hypothetical cause of hypertension during the treatment with GnRH-a may be overweight or obesity. It is well known that general and central obesity are predisposing factors for hypertension and it is suggested that BMI and obesity are strong predictors of childhood elevated blood pressure [11]. In this case, medical treatment is, at first, not suggested, while physicians should establish a comprehensive management program emphasizing appropriate nutrition, exercise and behavioral modification. Nevertheless, the BMI of our patient did not increase during the treatment, so this hypothesis has low clinical significance.

Our patient was diagnosed with CPP and treated with GnRH-a every 4 weeks from the age of 7 until she was 10 years old. During the treatment, she showed typical and slight side effects, such as desultory headaches, hot flushes and emotional lability. However, she also developed arterial hypertension. Considering her normotensive condition before the therapy started, the reversibility of hypertension after the end of the treatment and the maintenance of good blood pressure values without antihypertensive drugs, we can assume that hypoestrogenism played a fundamental role in the development of her hypertension.

In conclusion, although the evidence of hypertension during treatment with GnRH-a is infrequent and the underlying mechanism is still not clear, we recommend physicians not only evaluate body weight, pubertal development, height velocity and bone age of infants with CPP during treatment with GnRH agonist, but also to routinely monitor their blood pressure.

Learning points

- Treatment with GnRH-a (triptorelin) may cause arterial hypertension;
- The onset of hypertension during treatment with GnRH-a (triptorelin) is slow and progressive over time;
- During treatment with GnRH-a, a strict follow-up is necessary in order to evaluate pubertal development, height velocity, BMI and blood pressure.

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References

1. Latronico AC, Brito VN, Carel JC. Causes, diagnosis, and treatment of central precocious puberty. Lancet Diabetes Endocrinol 2016;4:265–74.
2. Carel JC, Léger J. Clinical practice. Precocious puberty. N Engl J Med 2008;358:2366–77.
3. Carel JC, Eugster EA, Rogol A, Ghizzoni L, Palmert MR, et al. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. Pediatrics 2009;123:e752–62.
4. Antoniazzi F, Zamboni G. Central precocious puberty: current treatment options. Paediatr Drugs 2004;6:211–31.
5. Tonini G, Lazzerini M. Side effects of GnRH analogue treatment in childhood. J Pediatr Endocrinol Metab 2000;13:795–803.
6. Lurbe E, Agabiti-Rosei E, Cruickshank JK, Dominiczak A, Erdine S, et al. 2016 European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents. J Hypertens 2016;34:1887–920.
7. Calcaterra V, Mannarino S, Corana G, Codazzi AC, Mazzola A, et al. Hypertension during therapy with triptorelin in a girl with precocious puberty. Indian J Pediatr 2013;80:884–5.
8. Siomou E, Kosmeri C, Pavlou M, Vlahos AP, Argyropoulou MI, et al. Arterial hypertension during treatment with triptorelin in a child with Williams-Beuren syndrome. Pediatr Nephrol 2014;29:1633–6.
9. Albaladejo Blanco C, García Vicente JA, García-Faria Rialp F. Hypertension crisis as a side effect of triptorelin? Aten Primaria 2004;34:566–7.
10. Acs N, Szekacs B, Nadasy GL, Varbiro S, Kakucs R, et al. The effect of ovariectomy and oestrogen replacement on small artery biomechanics in the rat. Br J Obstet Gynaecol 1999;106:148–54.
11. Rosner B, Cook NR, Daniels S, Falkner B. Childhood blood pressure trends and risk factors for high blood pressure: the NHANES experience 1988–2008. Hypertension 2013;62:247–54.