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BRIEF REPORT

Arterial hypertension during treatment with triptorelin in a child with Williams–Beuren syndrome

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Abstract
Background Arterial hypertension (AHT) is a common finding in children with Williams–Beuren syndrome (WBS). Although cardiovascular and renal abnormalities can explain the AHT in some patients with WBS, its etiology is not fully understood and most cases are considered idiopathic.
Case-diagnosis/treatment The case is reported of a 10-year-old girl with WBS who developed severe AHT during treatment with triptorelin, a long-lasting gonadotropin-releasing hormone (GnRH) analog, administered because of early normal puberty. Comprehensive diagnostic studies ruled out other known causes of AHT associated with WBS. After discontinuation of triptorelin, the blood pressure remained within the normal range for her age and height with no antihypertensive treatment on long-term follow-up. To the best of the authors' knowledge, this is the first report of AHT associated with triptorelin administration in a child with WBS.
Conclusions Clinicians should be aware of the possibility, although rare, of AHT developing during triptorelin administration in childhood, specifically in patients at increased risk of AHT, such as those with WBS.

Keywords Williams–Beuren syndrome · Arterial hypertension · Triptorelin · Precocious puberty · Gonadotropin-releasing hormone (GnRH) analog

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Background

Williams–Beuren syndrome (WBS; OMIM # 194050) is a rare multisystem disorder caused by heterozygous deletion of ~1.6 Mb of the chromosome sub-band 7q11.23 [1]. Although population-based data on the occurrence of WBS are limited, studies suggest a prevalence of 1 per 7,500 to 1 per 10,000 individuals [2, 3].

Children with WBS are at risk for cardiovascular disease, specifically elastin arteriopathy, resulting in stenosis of the medium- and large-sized arteries, including supravalvular aortic stenosis (the most clinically significant and the most common cardiovascular finding), peripheral pulmonary arterial stenosis and renal artery stenosis, and arterial hypertension (AHT) [3–5]. They are also at risk for endocrine abnormalities, such as idiopathic hypercalcemia, hypercalciuria, hypothyroidism, and central precocious puberty [4, 5].

Triptorelin is a long-lasting gonadotropin-releasing hormone (GnRH) analog that has been used in precocious puberty [6], since its continuous administration suppresses pituitary gonadotropin secretion [7]. GnRH safety and tolerability in childhood and early adolescence has been documented, and GnRH treatment was found not to adversely affect body mass index, body mineral density, and not to predispose for polycystic ovary syndrome or menstrual irregularities in the long-term follow-up [6]. However, a recent study has associated the presence of AHT with the administration of triptorelin [8].

We report the case of a 10-year-old girl with WBS who developed severe AHT during treatment with triptorelin, administered because of early normal puberty. To the best of our knowledge, this is the first report of AHT associated with triptorelin in a child with WBS.

Case report

A 10-year-old female patient with WBS was referred to the pediatric nephrology department because of recently detected

AHT. Multiple measurements by her pediatrician showed systolic/diastolic blood pressure (BP) in the range of 140-155/85-110 mmHg (95th percentile for the child's age and height: 116/77 mmHg). Normal BP (range, 105-110/65-75 mmHg) had been recorded in all the child's previous monitoring visits to the pediatric nephrology outpatient clinic (at least three measurements of BP every 6–8 months during a 3-year interval), the most recent measurement being 8 months earlier. The patient had previously been attended to in the pediatric nephrology outpatient's clinic because of her history of nephrocalcinosis. No family history of AHT was reported in first-degree relatives.

The diagnosis of WBS had been made at the age of 1.2 years, based on the distinctive facial features: depressed nasal bridge with small upturned nose, long philtrum, wide mouth with prominent lower lip, malar hypoplasia with droopy cheeks, strabismus and a starburst eye pattern, and was established by FISH analysis (deletion at the 7q11.23 chromosome). The child showed moderate intellectual disability [average intelligence quotient (IQ) 48 on WISC III test], attention problems, and a characteristic personality of overfriendliness. Endocrine disturbances were also detected, including hypercalcemia, nephrocalcinosis, and hypothyroidism (low serum T4 and raised TSH concentrations) presenting in infancy, for which she had been receiving thyrohormone replacement. The pediatric endocrinological monitoring was conducted in another hospital, where early normal puberty had also been diagnosed at the age of 7 years, based on presentation with pubic hair of Tanner stage II development, bone age 8 years, with normal hypothalamus/pituitary magnetic resonance imaging (MRI), and she was being treated with triptorelin from the age of 9.5 years at a dose of 3.75 mg/4 weeks intramuscularly.

Findings on admission were: BP 155/110 mmHg in the right upper limb, heart rate 117/min, body weight 36.5 kg (50th percentile), height 133 cm (10th percentile), a soft systolic cardiac murmur 2/6, and symmetric pulses. The remaining physical examination was normal apart from the phenotypic features of WBS. Renal function, blood electrolyte, thyroid function, and hematological tests were within normal limits and urine analysis was negative for erythrocytes and protein. Retinal findings, electrocardiography and echocardiography imaging, Doppler, and abdominal ultrasound scan were all normal. Plasma renin activity in a supine position was 0.5 ng/ml/h (normal range, 0.2-1.4 ng/ml/h) and serum aldosterone 31.8 ng/dl (normal range, 3–28 ng/dl). Magnetic resonance angiography showed mild narrowing in the proximal left renal artery, but renal arteriography revealed no stenosis. The levels of adrenocorticotropic hormone (ACTH), cortisone in blood, free cortisone in 24-h urine collection, adrenaline, and noradrenaline in blood and 24-h urine collection were within normal limits.

The child had close BP monitoring in the pediatric nephrology department, where multiple measurements of BP (both during the day and night) for four consecutive days documented severe AHT (range, 140-155/85-110 mmHg). Ambulatory BP monitoring was not available at that time in our department due to technical reasons. Due to the severe AHT induction of antihypertensive treatment was started with amlodipine in two divided doses of 0.3 mg/kg/24 h, and atenolol at two divided doses of 2 mg/kg/24 h. Ambulatory BP monitoring on the 14th day of antihypertensive treatment revealed mean 24-h systolic/diastolic BP 111/67 mmHg (95th percentile for mean 24-h systolic/diastolic BP: 117/75 mmHg), mean daytime and nighttime systolic/diastolic BP 114/69 and 100/61 respectively, nocturnal dipping 12 %, and systolic BP load 30 %, which constitutes AHT stage I [9].

Triptorelin therapy was discontinued 1 year later (total duration of treatment 1.5 years). Ambulatory BP monitoring 3 months after cessation of triptorelin treatment showed normal BP levels with the child on the same anti-hypertensive treatment. Gradually, discontinuation of atenolol and amlodipine was instituted and fully stopped 4 and 6 months later, respectively. Two-year monitoring showed normal BP levels with a range of 105-110/70-75 mmHg on multiple measurements, with no further antihypertensive treatment.

Discussion

We report the case of a 10-year-old female patient with clinically and genetically typical WBS who presented severe AHT 6 months after the induction of triptorelin therapy for early normal puberty, having been previously normotensive.

Precocious puberty has an estimated prevalence of 18.3 % among children with WBS [10]. Triptorelin is a GnRH analog that has been used in central precocious puberty since its continuous administration suppresses pituitary gonadotropin secretion [7]. After an initial "flare-up" of secretion of luteinizing hormone (LH) and folicle stimulating hormone (FSH), their levels ultimately decrease, due to desensitization of the pituitary GnRH receptors. This action results in decreased gonadal sex steroid levels with cessation of secondary sexual development and menstruation in girls [7]. Our patient had early normal puberty at the age of 7 years (pubic hair of Tanner stage II development and bone age 8 years) for which she received triptorelin therapy from the age of 9.5 years for 1.5 years. She reached menarche at the age of 11.5 years, six months after the discontinuation of triptorelin. Cherniske and colleagues [11] reported that puberty in WBS occurred earlier than in the control population (90 % of females reached menarche prior to the age of 12 years). They also noted that the sequence of pubertal development was normal and bone age was always consistent with, or in excess of chronological age, which is in agreement with the present case.

The prevalence of AHT in patients with WBS ranges from 5–70 % [5]. Defects in the elastin genes, leading to elastin

haploinsufficiency, underlie the observed arteriopathy. The reduced elastin synthesis leads to increased proliferation of vascular smooth muscle cells both in vivo and in organ cultures [3]. This contributes to the development of aortic supravalvular stenosis, coarctation of the aorta, and renal artery stenosis. These cardiovascular abnormalities, along with renal defects such as renal hypoplasia, renal agenesis, and multicystic kidneys, can explain the presence of AHT in some patients with WBS [3, 5]. In this patient, echocardiography imaging, Doppler and abdominal ultrasound imaging, renal vascular angiography and endocrine studies were normal, excluding overt cardiovascular/renovascular disease, renal parenchymal disease, and endocrine causes of AHT. Although the etiology of AHT in WBS is not fully understood and most cases are considered idiopathic, all the patients studied were found to have histological vascular abnormalities and arterial wall thickening, which led to the hypothesis that decreased compliance of the arterial tree is a factor in AHT in WBS [3]. Furthermore, genetic factors may contribute to the presence of AHT in patients with WBS. Del Campo and colleagues [12] reported that the loss of a functional copy of *NCF1*, a gene coding for the p47(phox) subunit of the NADPH oxidase, has a protective role against AHT in a proportion of patients with WBS, likely through a lifelong reduced angiotensin II-mediated oxidative stress. In this patient, although it was apparent that the AHT appeared 6 months after initiation of triptorelin treatment for her early normal puberty, it was initially thought to be associated with a possible decrease in arterial compliance known to occur in WBS patients, and triptorelin administration was continued. In view of the persistence of normal BP values without antihypertensive drugs long after the ultimate discontinuation of triptorelin, in combination with the normal BP levels recorded before triptorelin administration and the exclusion of other known associated causes with AHT in WBS, an association could be speculated between AHT and the use of triptorelin in our patient.

The low estrogen levels induced by triptorelin in association with the vascular abnormalities in patients with WBS may lead to the development of AHT. In experimental studies, a hypertensive crisis has been described during triptorelin treatment, which was attributed to hypoestrogenism [13]. Animal studies have shown that a low estrogen level following pharmacological ovariectomy by triptorelin decreases the passive diameter of small peripheral arteries [14] and venous capacitance function and distensibility [15]. These changes may play a role in the development of AHT and venous varicosity, which could possibly be prevented by estrogen substitution [14, 15]. AHT during therapy with triptorelin has previously been reported in a 7-year-old girl with precocious puberty, and the authors speculated that hypoestrogenism induced by the treatment may play a role in the elevation of BP levels [8]. To the best of the knowledge of the authors, this is the first report of AHT associated with the use of triptorelin in a child with WBS. However, based on the available literature, it is difficult for us to reach a conclusion about how often triptorelin may cause AHT.

Conclusions

In conclusion, although the occurrence of AHT during GnRH treatment is not a new observation, it is still not clear whether its frequency is higher in WBS, a hypertension prone population, than in the general population. In the light of the not infrequent use of GnRH in children with WBS, clinicians should take note of this potential complication.

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