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Case Report

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Arterial hypertension as a complication of triptorelin treatment in adolescents with gender dysphoria

Abstract

Background: Adolescents with gender dysphoria are treated with gonadotropin releasing hormone analogues (GnRHa) as part of the gender reassignment procedure. The mid- and long-term health effects of this treatment are not known.

Cases: Three cases of arterial hypertension were observed in natal girls with gender dysphoria during GnRHa treatment with triptorelin. Hypertension was demonstrated by ambulatory blood pressure monitoring (ABPM). In the first case, GnRHa therapy was stopped and blood pressure normalized. On restart, hypertension reoccurred and anti-hypertensive medication was initiated while continuing GnRHa. In the second patient, GnRHa was discontinued leading to normalization of blood pressure. In the third case GnRHa was continued and anti-hypertensive medication was prescribed.

Conclusion: Early GnRHa treatment in adolescents with gender dysphoria using GnRHa is important for their emotional and social well-being but may induce arterial hypertension, possibly due to estrogen depletion. The clinical implications of our observation for the medical treatment of gender dysphoria patients need to be investigated. Also, vigilance for high blood pressure in other pediatric populations treated with GnRHa is warranted, preferably using ABPM.

Keywords: hypertension, gnrha, sex reassignment procedures, estrogens, adverse event

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Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure, CSH, cross-sex hormones, GNRHA, gonadotropin releasing hormone analogue

Introduction

Adolescents with gender dysphoria experience incongruence between their assigned and their experienced gende.[1] Gender reassignment therapy aims to achieve transition to the desired gender and includes psychological, hormonal and surgical interventions. Puberty can be suspended using gonadotropin releasing hormone analogues (GnRHa) thus preventing development in the direction of the natal gender and gaining time to explore the patient's wish for later gender reassignment. Subsequently, hormones of the desired sex–cross-sex hormones (CSH) – are added. Natal girls with gender dysphoria (so-called transboys) receive testosterone. Finally, during sex-reassignment surgery the gonads are removed and GnRHa therapy is discontinued.[2]

GnRHa suppress LH and FSH and thereby induce a marked inhibition of gonadal activity. Since 1981, GnRHa administration has been the standard treatment for central precocious puberty (CPP) This treatment is generally considered to be safe and well tolerated in children and adolescents.[3]

Adolescents with gender dysphoria have only been treated with GnRHa since 2000 and long-term effects in this population are yet unknown. Recently, two cases of GnRHa induced hypertension in the pediatric population have been published, one in a 7-year-old girl with central precocious puberty[4] and the other in a ten-year-old girl with Williams-Beuren syndrome and early puberty.[5]

Here, we present three cases of GnRHa induced arterial hypertension in adolescent natal girls with gender dysphoria. To the best of our knowledge this is the first report of GnRHa induced arterial hypertension in healthy individuals.

Case presentation

Patient characteristics at start of GnRHa treatment and subsequent development of hypertension are summarized in Table 1.

Case 1

GnRHa treatment with triptorelin was started during early puberty at the age of 11.8 years. During follow up visits blood pressure (BP) gradually increased, but was thought to be elevated due to the white coat effect. After 16 months of GnRHa treatment 24-hour ambulatory blood pressure monitoring (ABPM) was performed, which demonstrated arterial hypertension. A diagnostic work-up showed papilledema and elevated intracranial pressure (29 cmH_2O) with a normal MRI scan. Kidney function and renal ultrasound including Doppler studies were normal. Endocrine studies excluded pheochromocytoma and hyperaldosteronism. GnRHa was discontinued and benign intra-cranial hypertension was treated with a short course of acetazolamide. After 3 months BP had normalized but puberty had progressed to Tanner stage B3. It was decided to resume GnRHa treatment under close monitoring of blood pressure and frequent fundoscopy. Hypertension reoccurred and was treated with nifedipine and labetalol, while increased intracranial pressure did not reoccur.

Table 1: Blood pressure development during gonadotropin releasing analogue (GnRHa) treatment in natal girls with gender dysphoria.

	At start GnRHa						During GnRHa		After stop GnRHa		After restart GnRHa	
	Age (y)	**Height (SDS) (cm)**	**BMI (SDS) (kg/m2)**	**Tanner stage**	**BP (percentile) (mmHg)**	**ABPM (SDS) (mmHg)**	**BP (percentile) (mmHg)**	**ABPM (SDS) (mmHg)**	**BP (percentile) (mmHg)**	**ABPM (SDS) (mmHg)**	**BP (percentile) (mmHg)**	**ABPM (SDS) (mmHg)**
Case1	11.8	144.0 (-1.6)	15.4 (-1.0)	B2,P3	115/80 (P88/P96)	-	144/103 (P100/ P100)	24 hour	133/87 (P99/P98)	24 hour	140/82 (P100/P96)	24 hour
								124/71 (+2.1/+0.8)		104/71 (-0.9/+0.8)		
								Diurnal 125/74 (+1.4/+0.3)		Diurnal 106/75 (-1.1/+0.5)		Diurnal 129/74 (+2.6/+1.3)
								Nocturnal 117/61 (+2.1/+1.0)		Nocturnal 101/52 (+0.3/-0.5)		Nocturnal -
Case2	18	155.4 (-2.2)	22.6 (+0.7)	B5,P5	117/71 (P82/P72)	-	155/84 (P100/P96)	24 hour 142/88 (+4.6/+3.9)	136/66 (P100/P60)	24 hour 120/78 (+1.3/+2.0)	-	-
								Diurnal 144/91 (+3.8/+3.3)		Diurnal 124/81 (+1.1/+0.5)		
								Nocturnal 124/71 (+2.8/+2.4)		Nocturnal 99/58 (-0.1/+0.6)		
Case3	12.5	171 (+1.9)	20.9 (+1.2)	B4,P4	125/58 (P93/P26)	24 hour 116/60 (+0.2/-1.7)	137/76 (P99/P82)	24 hour 132/76 (+2.2/0.0)	-	-	-	-
						Diurnal 120/64 (0.0/-1.8)		Diurnal 134/74 (+2.2/0.0)				
						Nocturnal 101/64 (-0.3/+1.0)		Nocturnal 119/55 (+2.3/0.0)				

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Case 2

Triptorelin therapy was started at the age of 18 years in a natal girl with gender dysphoria. After 3 months of GnRHa therapy elevated BP was noted during a visit to the outpatient clinic and hypertension was confirmed with ABPM. Fundoscopy was normal. GnRHa treatment was stopped and lynestrenol, a progestagen, was given to prevent menses. After 1 month BP had normalized. Since the patient had reached sexual maturation, GnRHa was not restarted and the patient has remained normotensive.

Case 3

A 12.5 year-old natal girl with gender dysphoria developed hypertension after 3 months of GnRHa treatment. Triptorelin was continued and hypertension was treated with calcium antagonists.

Discussion

We observed three cases of arterial hypertension documented by ABPM during GnRHa treatment for gender dysphoria. Normalization of blood pressure after discontinuation of GnRHa in cases 1 and 2 and reoccurrence of hypertension after restart of GnRHa treatment in case 1 suggest a causal relationship. The benign intracranial hypertension in case 1 was probably related to the development of serious arterial hypertension as it was not observed in the other two patients and – in contrast to the arterial hypertension - did not recur after re-exposition to GnRHa. Our observations are in line with incidental reports on GnRHa therapy induced hypertension in children[4,5] and in adults.[6]

The mechanism by which GnRHa induces arterial hypertension is not clear. In our series and previous reports[4,5,6] all subjects were females with some degree of sexual maturation. This suggests that estrogen depletion may play a role in the pathogenesis. This is supported by animal studies reporting protective properties of estrogens on blood pressure. Dahl-sensitive rats carry a genetic mutation that induces hypertension when the rats are fed a high-sodium diet. Ovarectomy in female Dahl-sensitive rats resulted in accelerated development of hypertension which was reversible after administration of estrogens. By contrast, gonadectomy in male rats did not affect the development of hypertension.[7] In female Sprague-Dawley rats GnRHa administration lowered venous wall distensibility, which was restored by estrogens.[8]

According to the instructions for use issued by the manufacturer, arterial hypertension is considered an infrequent complication.[9] Therefore, the incidence of three cases in our patient population with gender dysphoria of 140 patients is remarkable. This may reflect increased awareness after identification of the index patient (case 1). Following the estrogen-withdrawal hypothesis, patients with gender dysphoria may be more prone to the development of arterial hypertension because they are treated at an older age and with more advanced pubery than children with central precocious puberty. Still, vigilance is also advisable in other pediatric patients who receive GnRHa. The diagnosis of hypertension in children can be challenging. Office BP measurements may be falsely elevated due to transient stress-induced hypertension (white coat hypertension), or falsely normal (masked hypertension). In those cases ABPM is mandatory to establish the diagnosis.[10]

Our observations are relevant for transgender health care as there is discussion whether adolescents with gender dysphoria should be treated with GnRHa and opponents are concerned about potential long-term side effects of such an intervention in an underage child. On the other hand, GnRHa treatment gives these adolescents time to reach a well-balanced decision to opt for the opposite sex while the development of irreversible secondary sexual characteristics is prevented. It has been demonstrated that the patients' psychological well-being benefits from GnRHa treatment and that patients experience less behavioural and emotional problems. Moreover, the effectiveness of this treatment protocol has recently been demonstrated in young adults who started and completed gender reassignment during adolescence.[1] In addition, in natal girls the effects of CSH need to be considered as testosterone may further increase BP. Indeed, in the adult transgender population adverse effects of gender reassignment treatment on cardiovascular health have been reported. Mortality did not seem to increase but a slight increase of blood pressure in combination with a decrease of arterial compliance has been observed in transmen (natal women with gender dysphoria). Also, in transwomen (natal men with gender dysphoria) more trombo-embolic incidents have been reported.[2]

Conclusion

GnRHa therapy may cause hypertension in natal girls with gender dysphoria, likely due to loss of the vasoprotective properties of estrogens. The clinical implications of these findings in transgender health care are unclear and future studies are warranted, including further investigations of the effect of GnRHa on arterial blood pressure. In addition, blood pressure should be monitored closely–preferably by ABPM–when GnRHa are prescribed.

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Conflict of interest

The author declares there is no conflict of interest.

References

1. de Vries AL, McGuire JK, Steensma TD, et al. Young adult psychological outcome after puberty suppression and gender reassignment. *Pediatrics.* 2014;134(4):696–704.
2. Hembree WC, Cohen–Kettenis P, Delemarre–van de Waal HA, et al. Endocrine treatment of transsexual persons: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2009;94(9):3132–3154.
3. Carel JC, Eugster EA, Rogol A, et al. Consensus statement on the use of gonadotropin–releasing hormone analogs in children. *Pediatrics.* 2009;123(4): e752–e762.
4. Calcaterra V, Mannarino S, Corana G, et al. Hypertension during therapy with triptorelin in a girl with precocious puberty. *Indian J Pediatr.* 2013;80(10):884–885.
5. Siomou E, Kosmeri C, Pavlou M, et al. Arterial hypertension during treatment with triptorelin in a child with Williams–Beuren syndrome. *Pediatr Nephrol.* 2014;29(9):1633–1636.
6. Bonfirraro G, Sanna B, De Marco A, et al. Use of a GnRH analogue in the treatment of certain forms of endometrial hyperplasia associated with menometrorrhagia]. *Minerva Ginecol.* 1995;47(10):467–470.
7. Hinojosa–Laborde C, Lange DL, et al. Role of female sex hormones in the development and reversal of dahl hypertension. *Hypertension.* 2000;35(1 Pt 2):484–489.
8. Acs N, Szekacs B, Nadasy GL, et al. Effects of combined sex hormone replacement therapy on small artery biomechanics in pharmacologically ovariectomized rats. *Maturitas.* 2000;34(1):83–92.
9. Bijsluiter Decapeptyl. Farmacotherapeutisch Kompas. Ref Type: Online Source. 2014.
10. Urbina E, Alpert B, Flynn J, et al. Ambulatory blood pressure monitoring in children and adolescents: recommendations for standard assessment: a scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee of the council on cardiovascular disease in the young and the council for high blood pressure research. *Hypertension.* 2008;52(3):433–451.

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