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CASE REPORT

MANAGEMENT OF RAPIDLY PROGRESSIVE PRECOCIOUS PUBERTY IN A PATIENT WITH MOSAIC TURNER SYNDROME

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Abstract

Context. Rapidly progressive precocious puberty (RPPP) is a rare condition in Turner syndrome (TS), with no consensus on treatment and follow-up. Only 12 cases have been reported so far.

Objective. We aimed to evaluate the effects of the GnRH analog (GnRHa) on growth and anti-mullerian hormone (AMH) levels in TS and RPPP.

Design. The clinical and laboratory data was recorded at baseline and after treatment.

Subjects and methods. An 8.1-year old girl with a karyotype of 45, X/46, XX presented with breast development at Tanner stage-2. Breast development advanced to Tanner stage-3 at the age of 8.7 years. Growth velocity (GV) was 8 cm/year. Bone age was 11 years with a predicted adult height of 152 cm. Luteinizing hormone (LH) was 1.69mIU/mL and estradiol was 33pg/mL, confirming the central puberty. AMH level was 6.33ng/mL. The sizes of ovaries and uterus were compatible with the pubertal stage, with an endometrial thickness of 5 mm. GnRHa was started for RPPP.

Results. After three months, GV declined to 0 cm/3 months and AMH level to 50% of the baseline. Growth hormone (GH) treatment was started for insufficient growth. GV improved with GH treatment, as well as a far more decreased AMH level.

Conclusion. GV usually declines before puberty in patients with TS, even if the mid-parental height is tall. RPPP should be considered if GV is increased. Excessive suppression of growth may be prevented with GH treatment. GnRHa treatment also plays a role in reducing AMH levels in patients with TS.

Keywords: GnRH analog, Rapidly progressive precocious puberty, Turner syndrome.

INTRODUCTION

Turner Syndrome (TS) is a constellation of signs and symptoms due to a partial or complete loss of one X chromosome. Short stature and gonadal failure are the two common features in TS (1,2). Whereas only 10-30% of the patients have spontaneous breast development; patients with 45,X/46,XX karyotype are suggested to have a higher rate of spontaneous menstruation (2,3).

The onset of puberty is marked by breast development in girls and commonly accepted age threshold to define precocious pubertal development is 8 years. Approximately 50% of those cases exhibit progressive puberty and short adult stature due to early epiphyseal fusion is one of the main concerns in this condition (4).

Rapidly progressive precocious puberty (RPPP) has been reported in only 12 patients with TS so far. The karyotype, age of pubertal onset, Tanner stage at diagnosis, midparental height, coexistence of short stature, or other features of TS were variable in these cases, but most of them had gonadotropin-releasing hormone analog (GnRHa) treatment with or without growth hormone (GH) therapy in order to avoid short adult height (5-14). We report here a case of TS with a 45,X/46,XX karyotype, who had a pubertal onset at the age of 8 years but progressing rapidly in the follow-up period and the results of the treatments including anti-Mullerian hormone (AMH) level which has not been previously discussed in previous cases.

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CASE REPORT

The patient was brought at the age of 3 years for routine control. She was diagnosed with TS prenatally and postnatal peripheral blood analysis demonstrated mosaicism with a 45,X/46,XX karyotype. She was born at the 36th week of gestation from non-consanguineous parents with a birth weight of 2750g. The medical history did not reveal a specific feature. Weight, height, and body mass index (BMI) percentiles according to the curves of Turkish patients with TS were 17.5 kg (97%), 98.8 cm (>97%), 17.9 (>97%), respectively. Pubertal status was Tanner stage 1 and no phenotypical feature of TS was observed. Cardiac, audiology, and renal examinations were normal. Thyroid function tests were within normal limits. Luteinizing hormone (LH level) was 0.01mIU/mL (1.8-11.78), follicle-stimulating hormone (FSH level) was 2.7mIU/mL (3.03-8.03), estradiol level was 36pg/mL (21-251).

At the age of 8.1 years, unilateral breast development with pubic hair at Tanner stage 2 without clitoromegaly was observed. Parents noticed that breast development had been present for 3 months. Weight was 38 kg (90-97%), height was 132.3 cm (>97%) and BMI was 21.8 kg/m^2 (90-97%) (Table 1).

At the age of 8.7 years breasts were at Tanner stage 3. Weight, height and BMI measures were 41kg (>97%), 136.3cm (>97%) and 21.8 (90-97%) respectively. Height progression on the chart was remarkable with a growth velocity (GV) of 8cm/year. The bone age was 11 years. A 6-year progression of bone age was recorded in the last 3 years. Predicted adult height (PAH) was 152 cm (90-97%) and targeted height was 162.2cm (midparental height SDS:-0.22). The maternal age of menarche was 12 years. Hormone levels were as follows; LH:1.69mIU/mL, estradiol:33pg/mL, AMH:6.33ng/mL (0.63-8.68). Thyroid function tests were within normal levels. Adrenal hormone levels excluded an adrenal pathology (Table 2). The right ovary was 4.1cm³, the left ovary was 4.8cm³ and uterus was 30x22x40mm (13.2cm³) in size, and a 5mm endometrium thickness was measured by supra-pubic ultrasonography. As the basal levels of LH and E2 were in pubertal ranges, a GnRH stimulation test was not performed.

Rapid progression in pubertal stage, bone age, hormone and ultrasonography findings suggested the diagnosis of RPPP. Brain and pituitary magnetic resonance findings were normal. The GnRHa treatment (triptorelin acetate) was started at the age of 8.7 years. At the third month of treatment, FSH level was 2.2mIU/mL, LH level was 0.54mIU/mL, estradiol level was <10pg/mL. At the 10th month of the treatment, the GV was reduced extremely (no growth in the last 3 months) and the AMH level declined approximately to %50 of the baseline value. Thus recombinant GH treatment with a dose of 0.045 mg/kg/g/day was added because of insufficient GV and positive effects of GH on ovarian functions and AMH levels; a GH stimulation test was not performed as TS was one of the indications for growth hormone treatment. The growth and BMI charts of the patients are shown in Figure 1. The clinical findings, hormone levels and treatments are summarized in Tables 1 and 2. The changes in AMH levels are shown in Figure 2. The menarche was started at the age of 11.5 years. An informed consent form for publication was given by the parents.

Table 1. The clinical findings of the patient

Age (years)	Height (cm) (%)	Weight (kg) (%)	BMI (%)	Puberty stage	Bone age (years)	PAH (cm)
3.1	98.8 (>97%)	17.5 (>97%)	17.9 (90-97%)	1	-	-
4.4	109 (>97%)	20.4 (90-97%)	17.2 (75-90%)	1	-	-
5.5	112.7 (>97)	25 (>97)	19.9 (90-97%)	1	5	
7.3	124.7 (>97%)	32.2 (90-97%)	20.9 (90-97%)	1	-	-
8.1	132.3 (>97%)	38 (90-97%)	21.8 (90-97%)	2	-	-
8.7	136.3 (>97%)	41 (>97%)	22.2 (90-97%)	3	11	152
9	138.5 (>97%)	43.8 (>97%)	22.8 (90-97%)	3	-	-
9.1	140.7 (>97%)	45.4 (>97%)	23.2 (90-97%)	2	-	-
9.5	140.7 (>97%)	48.9 (>97%)	24.8 (90-97%)	2	11-12	154
9.7	143.4 (>97%)	49.7 (97%)	24.2 (90-97%)	2	-	-
10	145 (>97%)	51.5 (>97%)	24.5 (90-97%)	3	12	157
10.1	146.9 (>97%)	52 (>97%)	24.1 (90-97%)	3	-	-
10.5	150 (>97%)	52 (>97%)	23.1 (90-97%)	3	12	162.5
10.8	150 (>97%)	54.2 (>97%)	24 (90-97%)	3	-	-
11	152 (>97%)	55 (>97%)	23.8 (90%)	3	-	-
11.3	153 (>97%)	54 (>97%)	23.1 (75-90%)	3	12-13	162.5

BMI: Body mass index, PAH: Predicted adult height.

Table 2. The hormonal findings and treatment of the patient

Age (years)	LH (mIU/mL)	FSH (mIU/mL)	E2 (pg/mL)	AMH (ng/mL)	IGF-1 (ng/mL)	IGFBP-3 (µg/mL)	Adrenal hormones	Treatment
3.1	<0.01	2.7	36	-	148	-	-	-
4.4	-	-	-	-	-	-	-	-
5.5	-	-	-	-	-	-	-	-
7.3	-	-	-	-	-	-	-	-
8.1	-	-	-	-	-	-	-	-
8.7	1.69	NA	33	6.33	416	5.61	Andros:0.31 ng/mL 17-OHP:1.28 ng/mL DHEAS: 141.9IU/mL TT: 0.23 ng/mL ACTH: 14 pg/mL	TA 3.75 mg depot 1x1 monthly
9	0.54	2.2	<10	-	207	-	-	LA 3.75 mg depot 1x1 monthly
9.1	-	-	-	-	-	-	-	LA 3.75 mg depot 1x1 monthly
9.5	-	-	-	3	242	6.61	-	LA + GH treatment 0.045 mg/kg/g/day
9.7	-	-	-	-	375	7.07	-	LA+GH treatment
10	2.69 (90th minute after LA injection)	4.32(90th minute after LA injection)	<10(90th minute after LA injection)	3.33	434	7.44	-	LA 3.75 mg 1x1à1x2 monthly + GH treatment
10.1	-	-	-	3.09	416	7.29	-	LA+GH treatment
10.5	0.24	1.73	20	5	391	8.48	-	LA+GH treatment
10.8	-	-	-	5.26	326	6.7	-	LA+GH treatment
11	0.47	2.87	23	6.7	355	7.1	-	Withdrawal of the treatments
11.3	5.15	4.75	23	6.7	339	6.7	-	-
11.6	-	-	-	-	-	-	-	Menarche

ACTH: Adrenocorticotropic hormone, AMH: Anti-Müllarian hormone, Andros: androstenedione, DHEAS: dehydroepiandrosterone sulphate; E2: estradiol, FSH: Follicle stimulating hormone, GH: Growth hormone, LA: Leuprolide acetate, LH: Luteinizing hormone, TA: Triptorelin acetate, TT: total testosterone, 17-OHP: 17-hydroxyprogesterone.

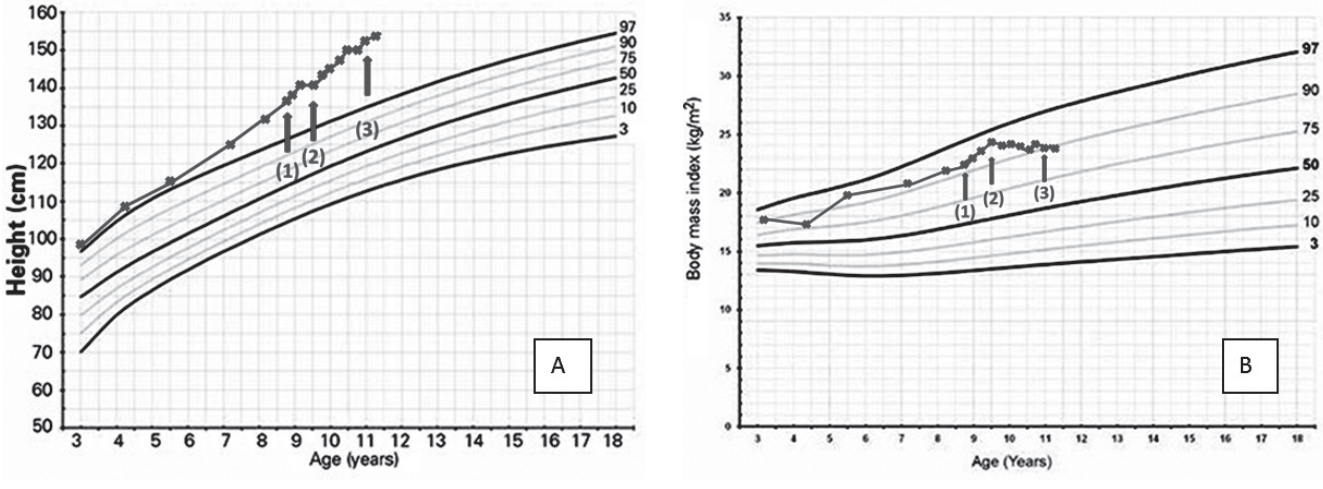

Figure 1. Growth (A) and body mass index (B) of the patient plotted on the chart of Turkish girls with Turner syndrome. 1: Start of triptorelin acetate treatment, 2: Start of recombinant growth hormone treatment, 3: End of the treatments.

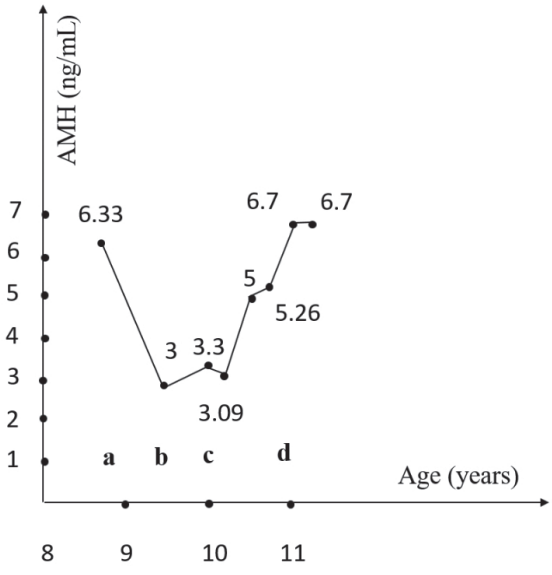

Figure 2. The graph showing anti-Mullerian hormone (AMH) level changes of the patient during follow-up. a: Start of triptorelin acetate treatment with a dose of 3.75 mg depot 1x1 monthly. b: Start of recombinant growth hormone treatment with a dose of 0.045 mg/kg/g/day. c: The dose increment of leuprolide acetate. d: End of the treatments.

DISCUSSION

Breast development started at the age of 8 years in our patient with mosaic TS. We have considered this case as RPPP according to the criteria recommended by Carel *et al.* (4), within these criteria; increased growth velocity, rapidly advancing bone age, rapid progression of physical and imaging findings as well as hormone levels, decreased predictive adult height were noteworthy.

In patients with TS, RPPP is not a common condition that has been previously reported in only 12 cases. In eight of these patients, the karyotype was mosaic as in our patient. However, the degree of X chromosome mosaicism, midparental height (MPH), height percentile at diagnosis, clinical findings, and outcomes were quite different (5-8,10,12,13). In our patient, the >97% of height, and absence of growth restriction before puberty was significant. The height of four previous cases with TS and RPPP was >90% at the time of diagnosis, as well (6,7,12).

When evaluated in terms of etiology, no endocrine disorder such as hypothyroidism and no central nervous system disorder were detected in our patient. We could not reach the pre-treatment FSH level because of technical problems, but its following levels were not increased. These findings removed us from the possibility of breast development due to an elevated FSH level associated with follicular insufficiency (7).

The treatments of the patients with TS and RPPP have also been different. One patient did not have any treatment; three patients had GnRHa and six patients were treated with GnRHa+GH treatment (6-11,12-14). There is no data on two patients (5,14). The increased GV and bone age advancement were taken under control mainly by GnRHa in some previous patients (6,7,14). In our case, GnRHa was started initially, and recombinant GH therapy was added afterwards. As expected, the GV of our case was normalized and IGF-1 levels decreased through average levels after GnRHa; however, PAH increased only 2 cm in 10 months. The patient presented by Evanchec *et al.* (6) had a final height of 164.4 cm with GnRHa but the MPH was 172 cm: quite higher than our patient's MPH. Otherwise, Sandal *et al.* (12) reported that the first year GV of their patient with GnRHa+GH treatment was 12 cm/year. Our patient had a GV of 9.3 cm/year with this combination, and at the end of the treatment we achieved an increase of 10.5 cm in PAH. We suggest that GH treatment was effective eventually in the increase of GV and PAH of our patient.

The prior issue in adults with TS is infertility. The AMH is specifically expressed in granulosa cells of growing nonselected follicles; and its level is a promising marker for ovarian function (16,17). In healthy girls, AMH levels rise during infancy and exhibit only minor fluctuations from childhood to early adulthood (17). In patients with TS, AMH levels correlate significantly with mosaic karyotype, spontaneous puberty, and negatively with FSH; whereas an AMH level <0.56 ng/mL predicts absent puberty or premature ovarian insufficiency (17-19). The AMH level of our patient with mosaic karyotype was similar to those of her healthy peers (0.63-8.68 ng/ml) (17). There is no data about AMH levels of other patients with TS and PP previously reported (5-14). It is remarkable in our case that AMH levels decreased to approximately 50% of the baseline level with GnRHa treatment and rested stable in time. Hagen *et al.* (21) revealed that the median level of AMH in girls with PP declines from 2.84 ng/mL to 1.46 ng/mL at the third month of GnRHa therapy. They have also reported that the AMH suppression was maintained after 12 months of treatment as in our patient. The etiology of this condition was not fully elucidated but it may be due to the slight decrease of individual AMH levels also shown in healthy girls during the first two years after pubertal onset or to partial responsiveness of AMH production to gonadotropins. However, our patient had TS. Although ovulation develops in some cases with

45,X/46,XX karyotype, early ovarian failure is generally inevitable; so it should be kept in mind that AMH values may decrease in time even in children with mosaic TS (16,17).

Another crucial issue is the effect of GH treatment on AMH levels. Visser *et al.* (18) reported that GH therapy increased 4.1 times the odds of having measurable AMH in TS. The GH/IGF-1 system may play an important role in ovarian follicular development and increase follicle viability (19). Though this was a cross-sectional study and individual differences may occur. We did not get an evident increase in AMH levels after GH treatment; however, it did not decrease more.

The AMH level of the patient after discontinuation of the treatments reached to baseline value. Hagen *et al.* (20) have also reported that the AMH levels of girls with central PP reduced at the early stage of the GnRHa, returned to pre-treatment levels after cessation, and concluded that the GnRHa therapy did not affect future reproductive function in those cases. This conclusion has also been promising for our patient's future reproductivity.

The main limitation, in this case, is that some data including bone age before RPPP and FSH level before treatment were absent because of technical problems.

In conclusion, RPPP is a rare condition in TS but it is important to monitor growth and to use growth-promoting therapies to prevent final height loss in these cases. The AMH levels may decrease during the treatments especially GnRHa; however, further studies on the long term follow-up of these patients are needed for more data about pubertal progression and fertility potential.

Conflict of interest

The authors declare that they have no conflict of interest.

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