

ORIGINAL

Serum FSH level below 10 mIU/mL at twelve years old is an index of spontaneous and cyclical menstruation in Turner syndrome

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Abstract. The gonadal function of patients with Turner syndrome (TS) is variable. Individuals with mosaicism characterized by 45,X/46,XX or 45,X/47,XXX are more likely to experience spontaneous menarche compared with other karyotypes. Prepubertal gonadotropins of TS patients with spontaneous menarche are reportedly normal or significantly lower than those of patients with induced menarche. The present study investigated an index of spontaneous and cyclical menstruation at 10-12 years old in TS. Subjects comprised 50 patients with TS, divided into three groups: Group A (n=7), with spontaneous menarche before 16 years old and regular menstruation for at least 1 year and 6 months; Group B (n=6), with irregular menstruation since menarche leading to secondary amenorrhea despite spontaneous menarche before 16 years old; and Group C (n=37), without spontaneous breast budding before 14 years old or without spontaneous menarche before 16 years old. Karyotype, LH and FSH concentrations at 10 and 12 years old were analyzed retrospectively. Spontaneous and cyclical menstruation was more frequently observed in TS with mosaicism characterized by 45,X/46,XX or 45,X/47,XXX than in TS with other karyotypes, as previously described. Spontaneous and cyclical menstruation in TS was observed when serum FSH level was <10 mIU/mL at 12 years old, suggesting this FSH level as an index of spontaneous and cyclical menstruation in TS.

Key words: Turner syndrome, Spontaneous and regular menstruation, LH, FSH, Karyotype

THE GONADAL FUNCTION of patients with Turner syndrome (TS) is variable. Approximately 20% of patients with TS show spontaneous menarche [1, 2]. Prediction of spontaneous and cyclical menstruation in prepubertal or early pubertal age is useful, to determine the necessity for hormone-replacement therapy (HRT) and the timing of HRT initiation. Individuals with mosaicism characterized by 45,X/46,XX or 45,X/47,XXX are more likely to experience spontaneous menarche compared with other karyotypes, with some exceptions [1,3-6]. Prepubertal gonadotropins of patients with spontaneous menarche are reportedly normal or significantly lower than those of patients with induced menarche [1, 3]. However, concrete cut-off levels of gonadotropins for predicting spontaneous and cyclical

menstruation in TS have yet to be established.

The aim of this study was to investigate whether karyotype, LH and FSH concentrations at 10-12 years old can predict spontaneous and cyclical menstruation in TS.

Subjects

Subjects comprised 50 patients who had been diagnosed with TS based on conventional G-banding analysis using peripheral lymphocytes (without Y fragment), and in whom retrospective analysis about menarche and menstruation cycle could be performed. These patients represented a subset of 80 TS patients who have been managed at Tokyo Metropolitan Kiyose Children's Hospital, the predecessor of Tokyo Metropolitan Children's Medical Center, from January 1982 to June 2006. Median age at the time of enrolment was 21 years (range, 13-30 years). Median duration of observation was 9 years (range, 1-23 years).

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Table 1 Karyotype distribution of Groups A, B and C

	45,X	Mosaicisms		Structural abnormalities of the second X	Total
		45,X/46,XX or 45,X/47,XXX	X-monosomy/cellular line with structural abnormalities of the second X		
Group A	0	5	2	0	7
Group B	0	0	2	4	6
Group C	13	3	20	1	37

Subjects were divided into the following three groups based on the presence of spontaneous breast development/ menarche and regular menstruation. The definition of the regular menstruation was the menstruation which was observed once a month. The definition of the irregular menstruation was that the interval between menstruations was more than two months or the menstruation was observed no more after menarche. Group A (n=7) consisted of TS with spontaneous menarche before 16 years old and regular menstruation for at least 1 year and 6 months. Group B (n=6) consisted of TS with irregular menstruation since menarche leading to secondary amenorrhea despite spontaneous menarche before 16 years old. Group C (n=37) consisted of TS without spontaneous breast budding before 14 years old or without spontaneous menarche before 16 years old. In Group A, menstruation occurred regularly throughout the observation period, except for one patient who developed secondary amenorrhea 2 years and 1 month after menarche. Median duration of menstruation in Group A was 4 years and 1 month (range, 1 year and 6 months to 10 years and 5 months).

Median age at the time of enrolment was 18 years (range, 13-25 years) in Group A, 24 years (range, 15-30 years) in Group B, and 21 years (range, 14-29 years) in Group C. Median chronological age at menarche was 12 years (range, 12-13 years) in Group A, and 14 years (range, 12-16 years) in Group B.

The protocol of this study was approved by the clinical study committee and the ethics committee of Tokyo Metropolitan Kiyose Children's Hospital.

Methods

1. Laboratory analysis

Karyotype was analyzed in blood lymphocyte culture in all patients. Serum LH and FSH concentrations data were retrospectively analyzed at 10 and 12 years old (before starting HRT or menarche) from

hospital records. If serum LH and FSH levels were checked several times a year, the maximal value was used in the analysis.

2. Hormone assays

Concentrations of LH and FSH were measured using ARCHITECT assay (Abott Japan, Tokyo, Japan). For LH, sensitivity was 0.07 mIU/mL, and inter-assay coefficient of variation (CV) and intra-assay CV were 3.6% and 3.1%, respectively. For FSH, sensitivity was 0.05 mIU/mL, and inter- and intra-assay CVs were 4.6% and 4.2%, respectively. Mean female prepubertal control values of serum LH and FSH from 5-10 years old (n=17) were as follows: LH, <0.07 mIU/mL (in all controls); and FSH (mean±SD), 2.41±1.12 mIU/mL (range, 0.80-4.41 mIU/mL).

Results

1. Karyotype (Table 1)

Karyotypes in subjects were as follows: 45,X, 13 patients (26.0%); mosaicism characterized by 45,X/46,XX or 45,X/47,XXX (X-monosomy and cellular line without structural abnormalities of the second X), eight patients (16.0%); mosaicism characterized by X-monosomy and cellular line with structural abnormalities of the second X, 24 patients (48.0%); and structural abnormalities of the second X, five patients (10.0%).

Spontaneous and cyclical menstruation was more frequently observed in TS with mosaicism characterized by 45,X/46,XX or 45,X/47,XXX than in TS with other karyotypes. Five of seven patients (71.4%) in Group A showed mosaicism characterized by 45,X/46,XX or 45,X/47,XXX (3 had 45,X/46,XX and 2 had 45,X/47,XXX). The remaining two patients had X-monosomy and cellular line with structural abnormalities of the second X. No patients with 45,X were present in Group A.

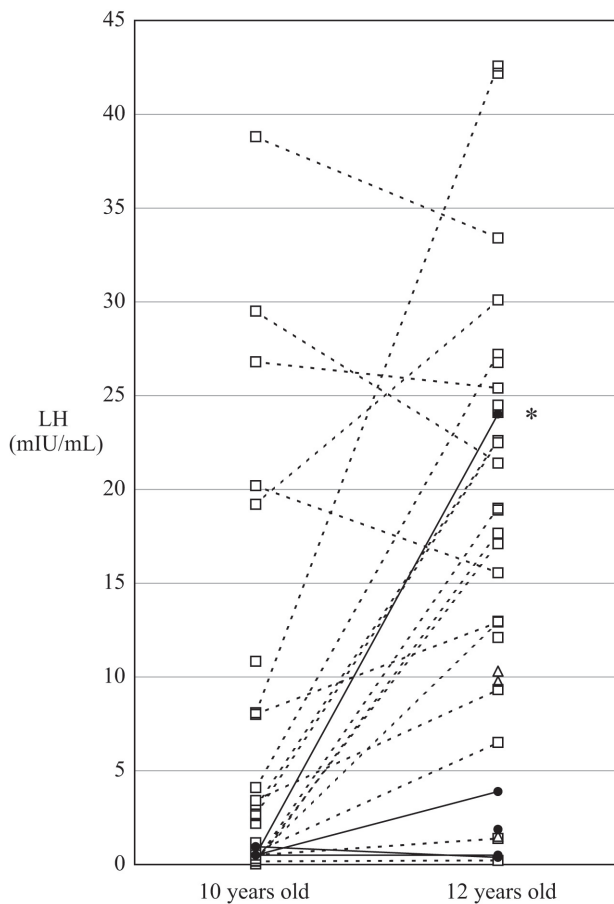


Fig. 1 Serum LH levels at 10 and 12 years old

Closed circle (●) with a straight line: Group A (10 years old, n=4; 12 years old, n=5). Asterisk shows a patient who developed secondary amenorrhea 2 years and 1 month after menarche. Serum LH level of this patient was 0.50 mIU/mL at 10 years old and 24.02 mIU/mL at 12 years old. Open triangle (△): Group B (10 years old, n=0; 12 years old, n=3). Open square (□) with a dotted line: Group C (10 years old, n=22; 12 years old, n=24).

2. LH (Fig. 1)

In Group A, serum LH levels were <5 mIU/mL at both 10 and 12 years old (0.50-0.95 mIU/mL at 10 years old and 0.38-3.89 mIU/mL at 12 years old), except for one patient who developed secondary amenorrhea 2 years and 1 month after menarche (asterisk in Fig. 1). In this patient, serum LH levels were 0.50 mIU/mL at 10 years old and 24.02 mIU/mL at 12 years old.

In Group B, serum LH levels were unavailable at 10 years old and 1.50-10.31 mIU/mL at 12 years old. In Group C, serum LH levels were 0.20-38.80 mIU/mL at 10 years old and 0.22-42.57 mIU/mL at 12

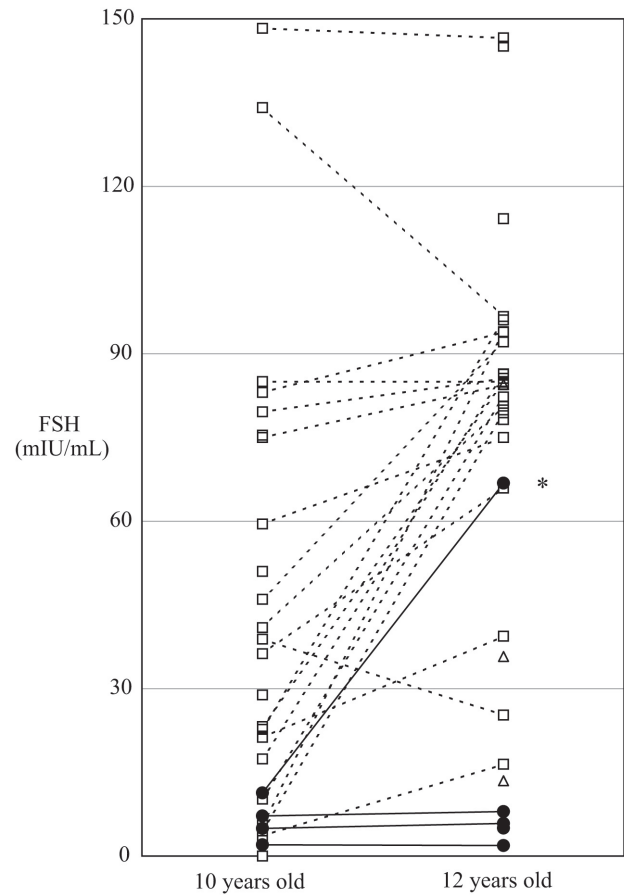


Fig. 2 Serum FSH levels at 10 and 12 years old

Closed circle (●) with a straight line: Group A (10 years old, n=4; 12 years old, n=5). Asterisk shows a patient who developed secondary amenorrhea 2 years and 1 month after menarche (the same patient shown in LH). Serum FSH level of this patient was 11.32 mIU/mL at 10 years old and 66.82 mIU/mL at 12 years old. Open triangle (△): Group B (10 years old, n=0; 12 years old, n=3). Open square (□) with a dotted line: Group C (10 years old, n=22; 12 years old, n=25).

years old. Serum LH levels were <5 mIU/mL at 12 years old in three patients in Groups B and C (Group B, 1 patient; Group C, 2 patients). Serum LH levels <5 mIU/mL were thus overlapped in Groups A, B and C.

3. FSH (Fig. 2)

In Group A, serum FSH levels were <10 mIU/mL at both 10 and 12 years old (2.02-7.20 mIU/mL at 10 years old; 1.90-7.98 mIU/mL at 12 years old), except for one patient who developed secondary amenorrhea (asterisk in Fig. 2; the same patient shown in LH). In this patient, serum FSH levels were 11.32 mIU/mL at 10 years old and 66.82 mIU/mL at 12 years old.

In Group B, serum FSH levels were unavailable at 10 years old and 13.50-84.50 mIU/mL at 12 years old. In Group C, serum FSH levels were 4.50-148.30 mIU/mL at 10 years old and 16.44-145.11 mIU/mL at 12 years old. Serum FSH levels were <10 mIU/mL at 10 years old in three patients of Group C. However, serum FSH levels for these three patients rose to >10 mIU/mL at 12 years old.

Spontaneous and cyclical menstruation in TS was thus observed when serum FSH level was <10 mIU/mL at 12 years old. No patients with serum FSH levels >10 mIU/mL at 10 years old or serum FSH levels rising to >10 mIU/mL from 10 to 12 years old showed spontaneous and cyclical menstruation. The patient in Group A whose serum FSH levels were >10 mIU/mL at 10 and 12 years old developed secondary amenorrhea 2 years and 1 month after menarche. In three patients with serum LH levels <5 mIU/mL at 12 years old in Groups B and C, serum FSH levels were 3.65-21.26 mIU/mL at 10 years old (n=2) and 13.50-39.38 mIU/mL at 12 years old (n=3). That is, serum FSH levels at 12 years old were >10 mIU/mL in these three patients.

Discussion

We investigated gonadotropins at 10 and 12 years old in this study, since mean chronological ages at breast budding and menarche were 10.0 ± 1.4 years and 12.3 ± 1.2 years, respectively, in Japanese females [7]. If spontaneous and cyclical menstruation can be predicted at these ages, decisions regarding the necessity for HRT and the timing of HRT initiation may not be delayed from the perspectives of psychosocial development and prevention of osteoporosis. Abnormally high gonadotropin levels in the neonatal or infantile periods are regarded as useful in detecting ovarian failure. However, a normal gonadotropin level in the neonatal or infantile period does not preclude a diagnosis of TS, as ovarian failure may progress in TS with age [8]. Since gonadotropin concentrations in TS between 4-10 years old resemble those in normal girls [9], ovarian failure cannot be diagnosed in TS children

before pubertal age.

The reason we set the cut-off level for serum LH at 5 mIU/mL was because serum LH levels in Group A were all <5 mIU/mL at 10 and 12 years old, with the exception of one patient who developed secondary amenorrhea. In the same manner, we set the cut-off level for serum FSH at 10 mIU/mL, as serum FSH levels of Group A were all <10 mIU/mL at 10 and 12 years old, with the except of the same patient mentioned above.

Karyotype and serum LH level were insufficient as indices for spontaneous and cyclical menstruation. Spontaneous and cyclical menstruation was more frequently observed in TS with mosaicism characterized by 45,X/46,XX and 45,X/47,XXX, consistent with previous reports [1, 3-6]. However, some TS patients with other karyotypes also showed spontaneous and cyclical menstruation. Although spontaneous menstrual cycles have reportedly been observed in TS with 45,X [1, 3, 5, 10-13], no patient with 45,X displayed spontaneous and cyclical menstruation in this study. Serum LH levels <5 mIU/mL overlapped in Groups A, B, and C.

The most useful index of spontaneous and cyclical menstruation in this study was serum FSH level. Spontaneous and cyclical menstruation is expected when serum FSH level is <10 mIU/mL at 12 years old in TS. If serum FSH level is >10 mIU/mL at 10 years old or serum FSH level rises to >10 mIU/mL from 10 to 12 years old, spontaneous and cyclical menstruation cannot be expected. Serum FSH level is considered useful for evaluating gonadal function, as FSH secretion is suppressed by follicle-produced inhibin [14]. In TS, serum FSH level reportedly correlates negatively with ovarian volume and the number of follicles [2, 15-17]. Moreover, serum FSH level <11 mIU/mL was recently reported as a predictor of follicles identified in ovarian tissue in TS [2]. Given that report and the present result, serum FSH level <10 mIU/mL may represent an index of residual ovarian function.

In conclusion, serum FSH level <10 mIU/mL at 12 years old appears to represent an index of spontaneous and cyclical menstruation in TS.

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