

The Relation between Karyotype Findings and Gonadotropin Levels in Pediatric Turner's syndrome Patients

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Abstract

Background

Abnormal pubertal development and fertility are among the frequent complications in Turner's syndrome. Although elevated level of gonadotropins in Turner's syndrome patients is well documented, the possible correlation with the karyotype findings and anthropometric features of patients is not clearly addressed. The present report aimed to evaluate the relation between the follicle-stimulating hormone (FSH) serum level and cytogenetic findings in Iranian Turner's syndrome patients.

Materials and Methods: Abnormal pubertal development and fertility are among the frequent complications in Turner's syndrome. Although elevated level of gonadotropins in Turner's syndrome patients is well documented, the possible correlation with the karyotype findings and anthropometric features of patients is not clearly addressed. The present report aimed to evaluate the relation between the follicle-stimulating hormone (FSH) serum level and cytogenetic findings in Iranian Turner's syndrome patients.

Results: The mean age of the Turner's syndrome patients was 9.78 years and most of the patients were mosaic for Turner syndrome (54.3%). Although the FSH level increased, there was not any significant different between the FSH level in the initial evaluation and the second evaluation within the entire study population ($P=0.605$). Among those who were mosaic for Turner's syndrome and those with 45,XO karyotype, the FSH level increased during the follow up ($P=0.476$, and $P=0.357$, respectively).

Conclusion

The present study demonstrated that although Turner's syndrome patients face abnormal FSH levels, there is not any significant relation between the cytogenetic findings as well as anthropometric characteristics including height, weight and BMI with the serum FSH levels.

Key Words: Follicle-Stimulating Hormone, Karyotype, Turner's syndrome.

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1- INTRODUCTION

Turner's syndrome is a sporadic and relatively common chromosomal disorder with considerable mortality and morbidity (1). Partial or complete absence of one X chromosome is the main cause of this genetic syndrome. While the Turner's syndrome is caused by partial or total loss of X chromosome, it has been demonstrated that more than half of Turner's syndrome patients are mosaic for the chromosomal disorder (2). These variable genotypes and X chromosome abnormalities are considered responsible for development of a wide range of clinical symptoms in these patients. Most of the Turner's syndrome patients develop characteristic symptoms since infancy including swollen hands and feet as well as hypo-plastic nails (3, 4). Other clinical manifestations including short stature, webbed necks, Cutis Laxa and hypertension develop late in life (3, 4).

Metabolic reproductive abnormalities including abnormal gonadotropin levels are considered as common comorbidities of Turner's syndrome resulting in abnormal reproductive potentials. Most of the patients with 45, XO genotype have complete loss of germline cells in infancy and only 5% have enough germline cells, leading to spontaneous menstrual cycles (5). Moreover, Turner's syndrome patients may develop adrenarche at normal age but ovarian failure and secondary amenorrhea in late childhood (6); while 30% of Turner's syndrome patients develop different stages of puberty, one fifth develop menarche and less than 10% could have spontaneous pregnancy (2).

Abnormal level of gonadotropins has been reported and increased level of both Luteinizing hormone (LH), and follicle-stimulating hormone (FSH) are reported in children with Turner's syndrome becoming normal or near normal during later stages of life (7). Although the abnormal pubertal development in

Turner's syndrome patients has been addressed in the literature, the correlation of gonadotropins and Turner's syndrome patients' phenotype and cytogenetic findings is not clearly understood. The present study aimed to evaluate the relationship between common anthropometric phenotypes and cytogenetic findings with serum FSH levels in pediatric patients with Turner's syndrome.

2- MATERIALS AND METHODS

2-1. Study design and population

The present retrospective study took place in pediatric department of Imam Reza Hospital (Mashhad, Iran) from Jun 2010 to Jul 2018. Turner's syndrome patients who had medical records in Pediatric department of Imam Reza Hospital and who were diagnosed to have Turner syndrome based on their clinical phenotype and cytogenetic analysis agreed to participate in the present study.

2-2. Methods

The anthropometric features, puberty stages based on the Tanner stage (8) as well as the FSH level (by enzyme immunoassay) were evaluated for every patient 2 times with at least one year interval. Then, the patients were grouped according to their cytogenetic study results into two groups; the first group as those having 45,XO and the second group as those who were considered to be mosaic for Turner syndrome based on their karyotype (including 45,X/46,XX; 45,X/47,XXX; 45,X/46,XX/47,XXX; 45,X/46,XY).

2-3. Measuring tools: Laboratory measurements

The serum FSH level was evaluated by enzyme immunoassay method. Moreover, the patients' karyotype results were obtained from cytogenetic analysis of 10-

15 peripheral lymphocytes stained by Giemsa banding method (9).

2-4. Intervention

Anthropometric measurements including patients' height, weight and body mass index (BMI) as well as FSH levels were recorded.

2-5. Ethical consideration

The present study was approved by Mashhad University of Medical Sciences Ethic Committee (ID-code: IR.MUMS.SM.REC.1394.378).

2-6. Inclusion and exclusion criteria

All Turner's syndrome patients who were diagnosed based on both clinical and cytogenetic studies and who were younger than 16 years old were enrolled in the present study. Patients who refused to complete the follow up visits or take the study interventions were excluded from the study.

2-7. Data Analyses

The anthropometric features, FSH level and the puberty status were then compared between the study groups. Comparison of

different variables among Turner patients with different karyotype was performed by Mann Whitney and Independent sample t-tests. The study data were analyzed by SPSS software (version 16.0), and P-value less than 0.05 was considered as statistically significant.

3- RESULTS

The mean age of the Turner's syndrome patients was 9.78 (4.13) years and most of the patients were mosaic for Turner syndrome (54.3%). The mean (SD) of height, weight and BMI at the first visit were 116.7 (24.75) cm, 28.78 (14.51) kg, and 19.05 (4.89) kg/m², respectively. During the initial evaluation of patients, 3 (9.7%) of 31 patients older than 9 years showed pubertal development. One of these 3 patients was in stage one of puberty and the rest were in the second stage. During the second evaluation, 3 patients were in the second stage, 5 were in the third stage and 2 others were in the fifth stage of puberty. Among these 10 patients, 4 of them developed puberty after receiving medical treatment (**Figure.1**).

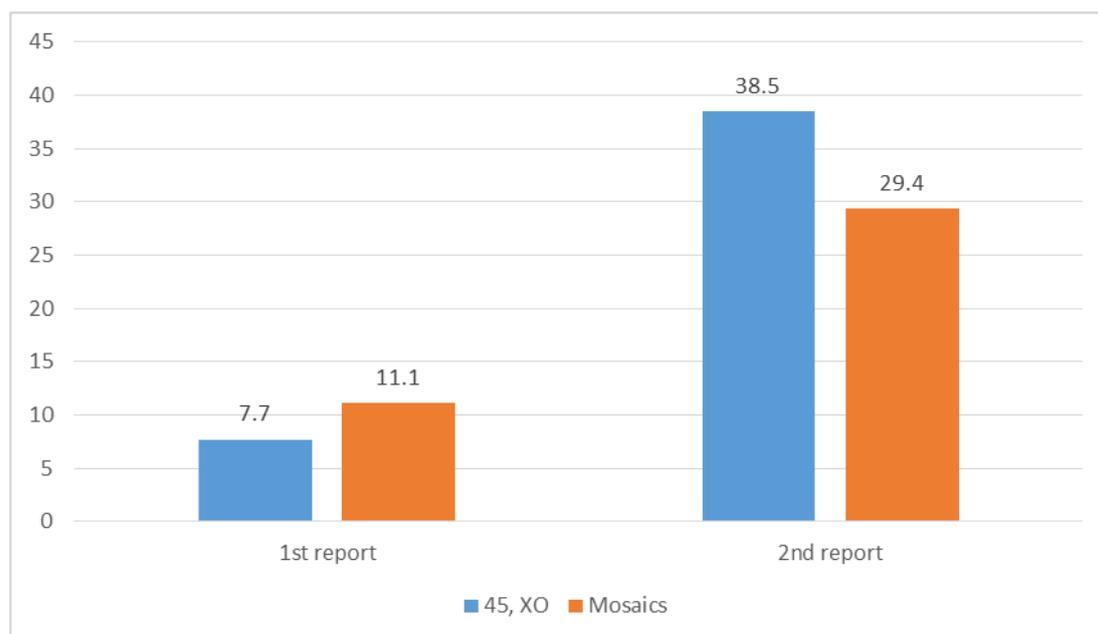


Fig.1: The percentage of pubertal development among patients with different karyotype findings.

During the initial evaluation, 5 patients (10.9%) had normal FSH level while the rest of the population had increased FSH level. Among these 5 patients, one patient was 45, XO and the rest of the patients were mosaic. During the second evaluation, 2 patients among 18 were 45, XO patients and 4 of 13 patients with mosaic karyotype for Turner's syndrome had normal FSH level (P=0.182). There was not any significant difference between the mean (SD) of FSH level in the initial evaluation (62.72 (56.13) U/lit) and the second evaluation (79.14 (94.47) U/lit)

within the entire study population (P=0.605). Among those who were mosaic for Turner's syndrome, the mean (SD) of FSH raised from 59.31 (55.59) U/lit to 60.49 (46.25) U/lit (P=0.476). Similarly, the patients with 45, XO karyotype showed increase in mean (SD) of FSH level during the study follow up (62.4 (58.1) U/lit to 92.61 (118.82) U/lit) (P=0.357). **Tables 1 and 2** compare the difference of weight, age, height, and BMI and FSH level between the participants with different karyotype findings.

Table-1: Comparison of different variables among Turner patients with different karyotype findings in the first visit and the second visit one year after.

Time of visit	Variables	45,XO group		Mosaic group		P value
		Mean	Standard deviation	Mean	Standard deviation	
1 st visit	FSH (U/lit)	62.4	58.1	59.31	55.59	0.877*
	Difference of FSH from normal level	56.1	56.89	53.64	53.41	0.878**
	Age (year)	9.47	4.34	10.04	4.02	0.65**
	Height (cm)	111.7	31.14	121	17.31	0.208**
	Weight (kg)	27.19	13.25	30.12	15.63	0.501**
2 nd visit	BMI (kg/cm ²)	18.53	4.02	19.49	5.55	0.364**
	FSH (U/lit)	92.61	1118.8	60.49	46.25	0.364**
	Difference of FSH from normal level	85.81	117.41	53.43	44.68	0.354**
	Age (year)	13.16	4.2	13.3	3.75	0.924**
	Height (cm)	121	31.89	125.15	36.8	0.74**
	Weight (kg)	33.97	12.81	40.26	15.45	0.225**
	BMI (kg/cm ²)	20.1	4.39	21.28	4.26	0.46**

*Mann Whitney test. **Independent sample t-test.

Table-2: Comparison of different variables among Turner's syndrome patients in their first visit and their second visit one year after.

Variables	Total patients		45, XO patients		Mosaic patients	
	1st visit	2nd visit	1st visit	2nd visit	1st visit	2nd visit
FSH (U/lit)	62.72±56.13	79.14±94.47	62.4±58.1	92.61±118.82	59.31±55.59	60.49±46.25
FSH level from normal (U/lit)	54.79±54.42	72.23±94.2	56.15±56.89	85.81±117.41	53.64±53.41	53.43±44.68
Weight (kg)	28.78±14.51	36.61±14.09*	27.19±13.25	33.97±12.81*	30.12±15.63	40.26±15.45*
Height (cm)	116.77±24.75	122.74±33.5	111.7±31.14	121±31.89	121±17.31	125.15±36.8
BMI (kg/m ²)	19.05±4.89	20.59±4.3*	18.53±4.02	20.1±4.39**	19.49±5.55	21.28±4.26*

*P<0.001, **P=0.015.

4- DISCUSSION

The main aim of the present research was evaluation of the relation between the cytogenetic findings and gonadotropin levels in Turner's syndrome patients. The present study demonstrated that although patients in 45, XO group had higher level of FSH in contrast to the mosaic group, the difference was not statistically significant. Moreover, after the follow up period, a similar difference was present but remained insignificant. Despite the well-defined clinical phenotypes of Turner's syndrome patients, the explanation behind the variable phenotypes among different patients is not clearly addressed. Variable cytogenetic findings among Turner's syndrome patients is considered as the possible cause of such variable clinical findings (10). Among the variable phenotypes, short stature is the consistent clinical finding among Turner's syndrome patients (10). While most of the patients are diagnosed by specific clinical phenotypes including short stature, performing cytogenetic analysis is considered to be an important diagnostic marker in almost all patients (11). From the aspect of cytogenetic view, the pure X chromosome monosomy is the most common finding in these patients (4).

Although the exact genotype-phenotype correlation in Turner's syndrome patients does not seem possible, it has been suggested that patients with complete X chromosome monosomy may have more severe phenotype and impaired reproductive function in contrast to mosaic patients (2). Moreover, the mosaics will be diagnosed later than 45, XO patients, meaning they are faced with increased risk of various comorbidities and reduced chance of pregnancy as it has been demonstrated that Turner's syndrome patients face abnormal oogenesis and apoptosis of fetal germ cells (12, 13). Therefore, it has been suggested that Turner's syndrome patients with

spontaneous menarche should be monitored carefully as providing delayed fertility preservation programs may result in losing the ovarian reserve (2). Even in Turner's syndrome, women with complete X chromosome monosomy could have successful ovarian response during ovarian stimulation which is due to possible ovarian mosaicism (2). Some reports provided evidences regarding successful spontaneous pregnancies among mosaic patients suggesting different prognosis for pregnancy of this syndrome with different cytogenetic findings (14). Further clinical studies confirmed the same finding indicating that approximately 40% of Turner patients may become pregnant (15). Various clinical studies evaluated the possible correlation between karyotype findings and development of spontaneous puberty in Turner's syndrome patients. Negreiros et al. demonstrated that approximately one third of patients with Turner's syndrome develop puberty spontaneously without medication (16). Zhong et al. demonstrated that the patients with complete X chromosome monosomy experience more delayed puberty in contrast to those who are mosaic (17).

However, the chromosomal content in this syndrome might not sufficiently predict the clinical features of patients (17). The other study by Hankus et al. demonstrated that approximately half of the Turner's syndrome patients develop spontaneous puberty and FSH is a predictor of spontaneous puberty in girls aged between 6 and 10 years old. Similar to our study, they reported that in Turner's syndrome patients, karyotype would not be able to determine the age of onset of menarche (18). Carpini et al.'s study reported that half of the Turner patients developed signs of puberty spontaneously and without medication (19). Moreover, they reported that none of the 45, XO patients developed spontaneous puberty while most of the patients who developed puberty

were 45, XO/XX (19). Regardless of the karyotype findings, FSH is considered as a predictive marker for successful oocyte cryopreservation (2). Even measurement of FSH in female children with unexpected short stature is recommended especially when performing cytogenetic analysis is not available (20). Similar to our findings, Carpini et al.'s study demonstrated that Turner's syndrome girls face increased level of FSH in contrast to healthy population with similar age until late childhood (20). Increased level of FSH in Turner's syndrome patients younger than 5 years old indicates ovarian failure (21).

Hagen et al. demonstrated that among Turner's syndrome patients, the FSH level follows a biphasic pattern before the age of 16 years (21); while some mosaic patients including patients with 45, XO/46, XX did not show abnormal FSH level during this time period, all the monosomic patients develop increased FSH level when they are younger than 5 years old and older than 10 years old (21). Aso et al. demonstrated that FSH level below 10 IU/ml is an indicator of spontaneous puberty in Turner's syndrome patients at the age of 12 years (22). Other studies suggested the serum FSH level below 6.7 IU/ml as a predictor of spontaneous menarche in girls aged between 6 and 10 years (18).

In contrast to our study demonstrating an insignificant increase in FSH level during the follow up period, Patricia Y et al. demonstrated that during their longer follow up period, Turner patients with 45, XO genotype show significantly increased FSH level (23). Moreover, they reported that FSH secretion pattern was significantly different among patients with complete X chromosome monosomy in contrast to those who were mosaic for Turner syndrome (23).

4-1. Study Limitations

The present study had some limitations that should be considered for future

researches. The limited sample size of the present study was the first important limitation. The second limitation was the limited follow up period of the patients as the gonadotropins tend to vary by age in Turner's patients. Moreover, the present study only relied on the FSH level as the main gonadotropin hormone while other hormones including LH could also be considered in future research.

5- CONCLUSION

Turner's syndrome is a common chromosomal abnormality presenting variable clinical phenotypes including abnormal level of gonadotropins. The present study demonstrated that although these patients face abnormal FSH levels, there is not any significant relation between the cytogenetic findings as well as anthropometric characteristics including height, weight and BMI with the serum FSH levels.

6- CONFLICT OF INTEREST: None.

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