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Original Article

Effects of Karyotype Variations on Phenotype of Patients with Turner Syndrome

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Abstract

Background: Turner syndrome (TS) is a sporadic disorder caused by the absence of all or some parts one X-chromosome with major developmental consequences such as short stature and ovarian failure etc. The minor manifestations of TS are cubitus valgus, micrognatism, high-arched palate, short and/or webbed neck, hypothyroidism, etc. Different karyotype abnormalities may lead to different clinical features; therefore, in this study we have tried to postulate karyotype-phenotype correlations in these patients.

Methods: In order to assess karyotype-phenotype correlations, 209 proven TS patients were studied and chromosomal analysis was performed on the basis of G-banding technique at high resolution.

Results: According to cytogenetic findings, karyotype abnormalities were classified into four groups: classic form 19%; mosaic form 76%; long arm isochromosome 4% and short arm deletion 1%. Clinical manifestations were more severe in classic TS rather than the other forms of chromosomal abnormalities.

Conclusion: The results of this study suggest that karyotype variations might affect phenotype of Turner syndrome. Therefore, chromosomal investigation for all suspected cases of Turner syndrome should be considered in order to approach an appropriate treatment protocol.
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Keywords ● Turner syndrome ● genotype ● phenotype

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Introduction

Turner syndrome (TS) results from complete or partial X monosomy.[1] TS is the most common chromosomal abnormality in females.[2] The incidence of TS is estimated as 3% of all females conceived,[3] and occurs one in 2000 to 5000 live-born girls.[3-6] The low incidence of this disorder may be the result of high fetal mortality rate. In fact, it is estimated that only one percent of embryos with a 45, X karyotype survive to term.[4]

TS embraces a broad spectrum of features such as sexual developmental deficiencies, improper ovarian functions, heart and/or kidney defects, webbed neck, low-set ears, and arthritis.[7-13] It also causes skeletal deformities including short stature, cubitus valgus and short fourth metacarpals as well as underactive thyroid glands, abnormal liver function, a propensity to ear infections and hearing deficits.[2,14-20] Many patients have hypoblastic or hyperconvex nails and excessive numbers

of nevi. Adults with TS have excessive rates of osteoporosis, hypertension, diabetes mellitus and experience high rates of morbidity and mortality.[8,11,13, 21-24] Almost all TS patients have short stature and loss of ovarian functions, but the severity of these problems varies considerably amongst individuals according to their karyotype.[3,5] Therefore, the objective of the present study was to postulate karyotype-phenotype correlations in patients diagnosed with Turner syndrome.

Patients and methods

Two hundred nine clinically diagnosed TS patients were introduced to the Department of Medical Genetic of Mashhad University of Medical Sciences, Mashhad, Iran, for cytogenetic analysis from 1981 to 2004. Chromosomal cultures were performed, according to the Armes Verma and Arvind Babu method.[25] Accordingly, 12 drops of whole peripheral blood were placed in a 5ml of full addition media (RPMI1640), supplemented with 20% fetal calf serum, penicillin and streptomycin. The cultures were incubated in slant position at 37^0C for 72 hrs. After that, 0.2ml of colcemid was added to each culture tube and then incubated at 37^0C for two more hrs. The culture tubes were centrifuged at 800 rpm for eight min. The supernatant was discarded and 5ml of 0.075M KCl was added to each culture tube, and then incubated for additional 15 min at 37^0C in water bath. All samples were centrifuged at 800 rpm for five min, their supernatants were discarded and the pellet cells resuspended in 5ml fresh fixative (3 part ethanol and one part acetic acid).

The tubes were centrifuged for five min, at 800 rpm, discarding the supernatant. These steps were repeated for three times and finally the pellet cells were resuspended in 0.5ml of fresh fixative. Then, 2 to 4 drops were placed on wet cold slide and their cells were treated with trypsin solution [10gr/100ml balanced salt solution) for 15 seconds at 37^0C and stained with Gimsa dye. The prepared slides were then studied under light microscope with high magnification (100×) for preparation of karyotypes. Each chromosome was analyzed for its presence and pairing chromosome in well-defined order, based on characterized band and number in order of size. The 23 pairs differed in the length of the arms and each show unique banding pattern.

Results

The results of chromosomal investigations from 209 patients with TS were according to Hall et al. were classified into four groups.[26] Group A consisted of 40 patient (19%) in classic Turner (45,X). Group B consisted of 152 patients (73%) in mosaic conditions of 45,X/46,XX, four patients (2%) in 45,X/46,Xi(Xq), two patients (<1%) in 46,XX/46X(Xp-). Group C consisted of nine patients (4%) with long arm isochromosome of X chromosome [46,Xi(Xq)]. Group D consisted two patients (<1%) with short arm deletion of X chromosome [46,X(Xp-)].

In this investigation, maternal and paternal ages were not important factors in the incidence of TS. Each group was clinically studied and their summarized features are presented in Table 1. The results showed that the clinical symptoms are more severe in classic form rather than other karyotype abnormalities.

Table 1: The Range of Major Clinical Manifestations as classic Turner (CT), mosaic Turner (MT), long arm isochromosome (LAI), and short arm deletion of X-chromosome (SAD) of Turner syndrome in relation to different karyotypes

	SS (%)	CV (%)	MG (%)	HP (%)	WN (%)	HT (%)	SN (%)	SM (%)	SO (%)	LH (%)
CT	100	68	41	77	82	4	64	41	23	59
MT	100	33	50	58	50	33	8	33	25	25
LAI	100	33	50	66	17	-	17	17	-	-
SAD	100	100	-	-	-	-	-	-	-	-

SS= short stature; CV= cubitus valgus; MG= Micrognatism; HP= High-arched Palate; WN= webbed neck; HT= hypothyroidism; SN= short neck; SM= short metacarpus; SO= secretory otitis; LH= low hair line

Discussion

Although clinical features of TS have been well defined, underlying genetic factors have not been clarified.[27] In this study, the frequency of karyotype- phenotype correlations have been considered (Table 1). Results from chromosomal investigations, appeared with 19% classic form, 76% mosaic forms, 4% long arm isochromosome and 1% short arm deletion. These findings strongly suggest that mosaic Turner syndrome is more compatible with life rather than classic form. These results are in agreement with the study of Held et al. demonstrating that mosaic conditions is more pronounced (66.7%) than classic one (20.7%).[28] On the other hand, in a similar study done by Suri et al. claimed that the incidence of classic Turner (44%) was greater

than mosaic TS (33%).[29] However, the identification of mosaicism depends directly on the methods of ascertainment.[30] One should think about the fact that mosaicism with a normal cell line, in the fetal membranes, might be necessary for adequate placental function and fetal survivals.[3,31] Therefore, all individuals with suspected TS should have a karyotype performed, and sufficient numbers of cells should be counted to exclude low percentage of mosaicism. It is also interesting to mention that our results, and the reports of Hall et al. and Globus et al. revealed that there was no correlation between the incidences of TS and maternal or paternal ages.[26,32]

According to data presented in Table 1, classic Turner (45, X) features were more severe than other forms of karyotypes. All patients were short in stature, as well as cubitus valgus, webbed neck, high-arched palate, short neck, short metacarpus, low hairline which were significantly more common in patients with the classic form (45,X). These results are are agreement with the reports of Gravholt et al. and Gunther et al. claiming some correlations existed between the karyotype and the phenotype of patients with TS.[33,34] In addition, hypothyroidism was more common in patients with mosaic form [45,X/46,XX and 45,X/46,Xi(Xq)]

Short stature and gonadal dysgenesis are two characteristics of the clinical features of the syndrome. Additionally, many organ systems and tissues may also be affected to a lesser or greater extent.[12, 28] The range of morbidities associated with the Turner syndrome seems to have a profound effect on quality of life of the patients.

Conclusion

It seems that there is a strong correlation between phenotype and karyotypes of Turners syndrome. Therefore, chromosomal analysis should be performed in all individuals with suspected TS in order to approach an appropriate treatment protocol.

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