Original Study

Frequency and Types of Chromosomal Abnormalities in Turkish Women with Amenorrhea

Osman Demirhan PhD *, Nilgün Tanrıverdi PhD, Erdal Tunç PhD, Nihal İnandıklıoğlu PhD, Dilara Süleymanova PhD, MD

Department of Medical Biology and Genetics, Faculty of Medicine, Çukurova University, Balcali-Adana, Turkey

A B S T R A C T

Study Objective: To estimate the frequency and the type of chromosomal abnormalities (CA) in patients with primary (PA) and secondary amenorrhea (SA).
Design: This retrospective study was comprised of patients had been referred to our laboratory between 1990 to 2008 and designed as original article.
Setting: Medical Faculty of Cukurova University in Turkey.
Participants: Chromosomal analysis was carried out on 393 patients with PA and SA that were referred to Cytogenetic laboratory of Medical Biology and Genetic Department, Faculty of Medicine, Çukurova University.
Interventions: Lymphocyte culturing depended karyotyping.
Main Outcome Measures: Standard lymphocyte culturing procedure and karyotyping was performed to all samples.
Results: PA and SA were identified in 393 patients. The karyotype was normal in 337 cases (85.8%) and abnormal in 56 (14.2%) patients. CAs were found in 54 (13.7%) and 2 (0.5%) of women with PA and SA, respectively. Females carrying rearrangements between autosomal and sex chromosomes were detected in 2% (8/393). The numerical abnormalities of the X chromosome were detected in 39.3% (22/56) (monosomy and mosaic). Structural abnormalities of the X and the other chromosomes were detected in 25.5% (13 of 56). Structural mosaicism of X chromosome was found in 5.4% (3 of 56). Male karyotype (46, XY) was found in 33.9% (19/56). The most frequently detected abnormality were X chromosome monosomies or mosaics.
Conclusions: Our study revealed that some causes of amenorrhea could be due to CAs. Therefore, cytogenetic study should be important test in the evaluation of patients with PA or SA. The most common abnormality seen is 45,X karyotype (monosomy X/Turner Syndrome) and its variants.
Key Words: Primary and secondary amenorrhea, Karyotyping, Chromosomal abnormalities

Introduction

Menstrual disorders are among the most commonly seen gynecologic problems in adolescent girls, composing 75% of such problems worldwide.[1] Amenorrhea means absence of menstruation during puberty or later in life. There are 2 types of amenorrhea: primary (PA) — the failure of menses to occur by the age of 16, and secondary (SA) — in which the menses appear at puberty but subsequently cease.[2] Amenorrhea is a symptom with several different causes, including pregnancy, absence of uterus and vagina, hormonal imbalance, excess of male testosterone, endometritis, improper functioning of ovaries,[3,4] and Müllerian agenesis. Cytogenetic investigations have shown the importance of chromosomal abnormalities (CAs) as a major cause of amenorrhea.[5,6] The percentage of CAs reported varies greatly, from 15.9% to 63.3% for primary amenorrhea[7–11] and from 3.8% to 44.4% for secondary amenorrhea.[4,8,11,12] This wide variation is due to different sample size of selection group or to the different selection criteria of different studies. A number of surveys in various parts of the world have endeavored to ascertain the contribution of sex CAs to the problem of amenorrhea. Many amenorrhea patients show a variety of CAs such as 45,X and sex reversals, that is, female phenotype with male chromosomal complements and also other autosomal translocations. This study was undertaken to determine the frequency and type of CAs that result in PA in the southern region of Turkey.

Materials and Methods

All women with PA and SA were recruited who were referred to our genetics laboratory from May 1, 1992, to April 28, 2009. Karyotypes of patients referred with amenorrhea were retrospectively analysed. The initial diagnosis of PA or SA as made by the referring gynecologist was followed up in the Division, based on the available medical history, which included clinical details, hormonal profile, and ultrasonography. PA was defined as the absence of menstruation and secondary sexual characteristics in phenotypic women aged 14 years or older, or aged 16 years or older. In SA cases, secondary sexual characteristics were present. Patients with SA had at least 1

The authors indicate no conflicts of interest.

* *Address correspondence to:* Prof. Dr. Osman Demirhan, PhD, Department of Medical Biology and Genetics, Faculty of Medicine, Çukurova University, 01330 Balcalı-Adana, Turkey; Phone: 90-322-3387140; fax: 90-322-3386572
E-mail address: osdemir@cu.edu.tr (O. Demirhan).

1083-3188/$ - see front matter
http://dx.doi.org/10.1016/j.jpag.2013.11.013

spontaneous bleeding episode, followed by no menstruation for a minimum of 12 months at or before the age of 42 years. Patients were referred to us from gynecology and other services for genetic analysis after exclusion of non-genetic causes. The age of the analyzed population ranged between 15 and 40 years and the average age was 19.3 years. The cytogenetic analyses were performed in the Cytogenetics Laboratory, at the Department of Medical Biology and Genetics, Faculty of Medicine, Çukurova University. Metaphase chromosome preparations from peripheral blood were made according to the standard cytogenetic protocols. Twenty metaphases were analyzed in all the patients, but in cases of abnormalities and mosaicism the study was extended up to 50 metaphases. All CAs were reported according to the current international standard nomenclature (ISCN, 2009).

Results

A total of 393 cases were evaluated for both PA and SA. The details of the karyotypes and percentage of abnormalities of all cases are given in Table 1. We had classified CAs into 3 main types with or without mosaicism. They are numerical and structural abnormalities of X chromosome, abnormalities of Y chromosome and females carrying rearrangements between autosomal and sex chromosomes.

The karyotype results were normal in 337 cases (85.8% of all cases). However, CAs was present in 56 (14.2%) of the cases with PA and SA (Table 1). These abnormalities was found in 54 (13.7%) and 2 (0.5%) of women with PA and SA, respectively (Table 1). The most frequent karyotype was X chromosome aneuploidy. X CAs (either structural or numerical) were found in 29 (7.4% of all cases and in 51.8% of all aberrations) patients. The most frequent abnormality detected was X chromosome monosomies or mosaics. The numerical abnormalities of the X chromosome were detected in 4.6% of all cases and in 32.1% of all aberrations. Structural abnormalities of the X chromosome were detected in 1.8% of all cases and in 12.5% of all aberrations. Mosaicism of X chromosome was found in 1% of all cases and in 7.1% of all aberrations. In those with PA, the second most common abnormalities was male karyotype (46,XY), which accounted for 19 (in 4.8% of all cases and in 33.9% of all aberrations) patients. Females carrying rearrangements between autosomal and sex chromosomes were detected in 2% of all cases and in 14.3 % of all aberrations. Two cases were found to have autosomal-sex chromosome translocations (Table 1).

Discussion

Amenorrhea is one of the important reasons for patient referral to an endocrine or gynecologic clinic. Its etiology is heterogeneous. Occurrence of CAs have a significant impact on both human fitness and sexual development. A large number of surveys have been undertaken worldwide in a bid to ascertain the frequency of CAs in patients who present with PA or SA. Majority of studies have had small patient numbers. In this study, we included a large number of patients. A review of the literature shows that CAs appear to be one of the main causes of PA. The estimated frequency in our study was compared with the CAs described in the literature and is presented in Tables 1 and 2.

In the present study, the karyotype was normal in 337 cases. The frequency of CAs was 14.3% which is comparable to other studies (Table 2). CAs were numerical and structural. The frequency of abnormal karyotypes has been reported to vary between 16% and 63.3% among women with PA in different parts of the world.[4,7] Our results (14.3%) were in accordance with other reports in similar studies: Joseph and Thomas,[9] 16%, and Rajangam et al,[5] 16.3%, and lower than in other studies[10,13–22] (Table 2). These findings show that CAs appear to be a cause of amenorrhea. When we looked at the wide scale of results from other studies, the

Table 1
Frequencies and Distributions of the Karyotypes in Patients with Amenorrhea

Cytogenetic Grade	Karyotype	No. of Cases	Frequency in all Cases (%)	Frequency in Aberrations (%)
The total number of cases with PA and SA		393 (371PA+22SA)		
Normal karyotypes	46,XX	337	85.8	
Abnormal karyotypes	Numerical and structural abnormalities	56 (54 PA + 2 SA)	14.2	
Abnormalities of X chromosome				
Pure Turner	45,X	18	4.6	32.1
Mosaic Turner with numerical aberrations of X	46,XX/45,X	4	1.0	7.1
Mosaic Turner with structural abnormalities of X	45,X/46,X,i(Xq)	2	0.5	3.6
Structural abnormalities of X	46,X,i(Xq)	4	1.0	7.1
Mosaic normal with structural abnormalities of X	46,XX/46,X,i(Xq)	1	0.5	1.8
Total		29	7.4	51.8
Abnormalities of Y chromosome				
Pure XY females	46,XY	16	4.1	28.6
Pure XY females with autosomal structural abnormalities	46,XY,inv(9)(p11-q13)	1	0.8	5.4
	46,XY,18q+	2		
Total		19	4.8	33.9
Females with autosomal and sex chromosome structural abnormalities	46,XX,fra(3q32)	1		
	46,XX,fra(1q32)	1		
	45,XX,robt(13; 14)	1		
	46,XX,inv(9)(p11-q12)	2		
	46,XX,15p+	1		
	46,XX,t(13; X)(q22; q28)	1		
	46,XX,t(8,X)	1		
Total		8	2.0	14.3