Trends in Medical Research

ISSN 1819-3587

Academic Journals Inc.

www.academicjournals.com

Trends in Medical Research 2 (4): 204-207, 2007
ISSN 1819-3587

Chromosomal Analysis of Girls with Short Stature and Puberty Failure

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Abstract: Short stature may be the normal expression of genetic potential, in which case the growth rate is normal, or it may be the result of a condition causing growth failure with a lower-than-normal growth rate. Short stature and puberty failure are primary characteristic of Turner Syndrome. The study was aimed to find out the chromosomal compliment of girls with suspected turner, having short stature and failure of puberty as phenotypic manifestations. Karyotype analysis was performed in 25 patients by standard procedures, using metaphase chromosome preparations from phytohemagglutinin stimulated blood lymphocytes. In each individual, conventional G-banding was also performed to obtain high resolution of banding pattern. 50% of the girls showed X-chromosome monosomy (45XO karyotype), 35% showed mosaicism 45XO/46XX and 10% showed structural abnormalities of X-chromosome, while 5% of the girls showed normal karyotype.

Key words: Turner syndrome, gonadotropin-releasing hormone, chromosome, karyotype, puberty, monosomy

INTRODUCTION

Short stature is the lower limit of normal for height at the 3rd and even the 4th percentile for age (Freeman *et al*., 1995). Puberty begins with increased pulsatile secretion of Gonadotropin-Releasing Hormone (GnRH) from the hypothalamus, increased pituitary responsiveness to GnRH, increased secretion of gonadotropins, gonadal maturation and increasing production of sex steroids. Puberty is considered to be clinically delayed if sexual maturation has not become apparent by age 13 years in girls (Bratberg *et al*., 2006). Nearly all of the body's hormones influence growth (Mohler *et al*., 2007). At puberty, both the sex hormones and growth hormone participate in producing the pubertal growth spurt; the ceasing of growth that follows this spurt is due primarily to the action of the sex hormones in closing the epiphyses (Carrel and Allen, 2000).

Short stature is a primary characteristic of Turner Syndrome. Turner Syndrome (TS) is a condition manifested in females who have only one X chromosome or a closely linked mosaic pattern of karyotype. Stature is partially r elated to the severity of X-chromosome structural alteration. X-chromosome monosomy (45XO karyotype) accounts for approximately 55% of TS patients, representing only 1% of all TS fetuses capable of surviving throughout gestation to term. Additionally, X-chromosome monosomy is the cause of 10% of all spontaneous abortions. Mosaicism, represented by 45XO/46XX or 45XO/47XXX cell lineages, has been detected in 30% of TS cases and is usually caused by paternal meiotic non-disjunction. Structural abnormalities of the X-chromosome are observed in 15% of TS patients, characterized by only one functioning short arm. The most common structural aberrations are the long arm isochromosome (46XiXq), the short arm deletion (46XdelX) and the X-ring chromosome (46XrX) (Elsheikh *et al*., 2001).

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Treatment with recombinant human growth hormone increases height velocity and ultimate stature in most but not all children (Ariceta and Langman, 2007). Many girls achieve heights of greater than 150 cm with early initiation of treatment. The best results of growth hormone treatment in girls with TS have been found if growth hormone therapy is initiated at age 4-5 years (Lanes, 2000). It is therefore imperative that females with TS be identified as promptly as possible so they may achieve the maximum benefits of growth hormone therapy. Any female with short stature must alert health care providers to the possibility of Turners Syndrome.

MATERIALS AND METHODS

This research study was carried out in the Department of Pediatric Genetics at The Children's Hospital and The Institute of Child Health, Lahore in the year 2005-2006. The patients in the study were referred to the Cytogenetics laboratory of this department for chromosome analysis from the Departments of Pediatric Endocrinology, Urology and Surgery. A total of 25 patients were included in the study (Turner Syndrome, 20; Causes other than chromosomal defect, 5).

Diagnostic Work up for the Patients

A Performa was designed which was filled for each patient. Comprehensive patient's history was taken along with details of mother's health and her pregnancy particulars including history of any drug intake during pregnancy. Detailed family history included parental consanguinity and check other patients with short stature and puberty failure in family.

The physical examination included the accurate measurement of the height and weight and thorough inspection and palpation of the external genitalia, the primary and secondary sexual characters and a search for the other congenital anomalies.

Karyotype Analysis

Karyotype analysis was performed in 25 patients by standard procedures, using metaphase chromosome preparations from phytohemagglutinin stimulated blood lymphocytes. In each individual, conventional G-banding was also performed to obtain high resolution of banding pattern.

RESULTS

Twenty five females ranging from 10 to 19 years with short stature and abnormalities of sexual development were referred for chromosome examination because of a clinical suspicion of Turner syndrome, to the Genetic counseling clinic and the Cytogenetic laboratory at The Department of Pediatric Genetics of The Children's Hospital and The Institute of Child Health Lahore. Karyotype analyses were carried out by standard methods in all Patients. Among 25 patients, 20 (80%) were diagnosed of Turner Syndrome and 5 (20%) were with normal karyotype, having some other causes rather than chromosomal defect. The patients under study were categorized into five groups on the basis of karyotype obtained; 10 (20%) patients were with 45, X chromosomal complement, 8 (32%) patients were having 45, X/46, XX, karyotype, 5 (20%) patients were with normal 46, XX chromosomal complement and 1 (4%) each with 46, XiXq and, 45, X /46XiXq karyotype (Table 1). Major phenotypic manifestations among the 25 patients were calculated to be as follows; menarche 8 (32%), webbed neck 17 (68%), wide carrying angle 19 (76%) and shield chest 20 (80%) (Table 2).

Tanner-Whitehouse growth charts were used for monitoring the growth and assessment of heights among the patients. Only girls with height below 3rd percentile or -2 standard deviation were included in the study. Accurate height, weight measurement along with standard deviation for that age were recorded (Table 3), deviations from the heights were ranged between -1.38 to -0.3. Then height was plotted against chronological ages. Mean Standard deviation from the mean heights was -0.8.

Table 1: Variations in the chromosomal constitutions among the patients (n = 25)

Karyotype	No. of patients (%)
45, X	10 (40%)
45, X/46, XX	8 (32%)
46, XX	5 (20%)
46, XiXq	1 (4%)
45, X/46, XiXq	1 (4%)
Total	25

Table 2: Major clinical findings in patients

Features	Frequency (%)
Menarche	8 (32%)
Webbed neck	17 (68%)
Wide carrying angle	19 (76%)
Shield chest	20 (80%)

Table 3: Distribution of heights among the girls with stature <3rd centile

Age (years)	Height (cm)
10	123.0
11	121.5
12	122.4
13	123.2
14	123.1
15	129.0
16	127.4
17	126.3
18	126.8
19	132.0

DISCUSSION

Turner syndrome is the major cause of short stature and puberty failure among the girls. Surveys over the last 30 years have indicated that short stature affects at least 95% of all individuals with Turner Syndrome. In another study carried out by Taback *et al*. (2002) among 180 short patients, 25 were known to have a known diagnosis consistent with short stature, such as trisomy 21, hypochondroplasia, Turner syndrome while eight children were diagnosed with an underlying disease as a result of the screening program, including Noonan syndrome, hypothyroidism, celiac disease, lead poisoning, neurofibromatosis and growth hormone deficiency and about 139 patients identified to have short stature were found to have an underlying medical condition that was previously undiagnosed in about 5% (Taback *et al*., 2002).

Sexual infantilism is one of the most common clinical findings in girls with Turner syndrome. Over 90% have gonadal failure. It is important to remember, however, that up to 30% of girls with Turner Syndrome will undergo spontaneous pubertal development and 2-5% will have spontaneous menses and may have the potential to achieve pregnancy without medical intervention (Hovatta, 1999). Pubertal development may be delayed and, in most patients, is followed by progressive ovarian failure (Forges *et al*., 2006). More than 50% of patients in one study had some breast development and some pubic and axillary hair is typical for most patients.

It was reported that pure 45, X monosomy (48%) is the most common karyotype and is associated with the most abnormal phenotype. In about two thirds of women with Turner syndrome, the normal X chromosome is maternal in origin (Jacobs *et al*., 1997). But in the present study we found that 40% of the girls were with 45, X karyotype and 32% were with 45, X/46, XX chromosomal complement.

All girls with short stature (less than the third percentile or below -2 SD on female growth curves), even those below 2 years of age, should have a karyotype performed if there are any features of Turner Syndrome present. Those who are more than 2.5 SD below the female growth curve should

have a karyotype performed regardless of the presence or absence of clinical features of Turner Syndrome. Apart from specific treatment, according to the under lying etiology, it is important to counsel parents. Children with short stature can have psychological stress due to negative comments from relatives, peers at school (Boman *et al*., 2004). If therapy is begun before the girl has deviated significantly from the normal growth curve, she will have a greater potential for catch-up growth and more height potential will remain. Estrogen replacement starting around age fourteen helps to maximize growth potential (Bondy, 2007). Cytogenetics studies are therefore a prerequisite, an advantage and imperative in girls with short stature and puberty failure.

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