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CASE REPORT / OLGU SUNUMU

Cytogenetic and clinical evaluation of two cases with 45,X/46,X,i(Xq) and 46,X,i(Xq) karyotype

45,X/46,X,i(Xq) ve 46,X,i(Xq) Karyotipi gösteren iki olgunun klinik ve sitogenetik yönden değerlendirilmesi

Etem Akbaş[1], Faik Gürkan Yazıcı[2], Hüseyin Durukan[2], Harika Topal[1], Nazan Eras Erdoğan[1]

ABSTRACT

In this study, cytogenetic and clinic findings of 46,X,i(Xq) and 45,X/46,X,i(Xq) which are the rare types of Turner syndrome are evaluated. Two patients were directed to the Cytogenetic Laboratory from Gynecology Clinic with chromosomal anomaly indication. Their peripheric blood samples are analyzed karyotypically using Giemsa-Tripsin Bantama method.

Case 1. The patient is 17 years old, has short height, a low-posterior hairline, short neck, small and wide apart breasts, normal external genitals and underdeveloped internal genitals. Her karyotype was 45,X/46,X,i(Xq).

Case 2. The patient is 19 years old, has primer amenore, short height, a low-posterior hairline, wide apart and underdeveloped breasts, normal external genitals, underdeveloped uterus, obscure ovarium. Her karyotype was determined to be 46,X,i(Xq). Although symptoms progress slightly weaker, our 45,X/46,X,i(Xq) and 46,X,i(Xq) cases, which are rare types of Turner Syndrome, are generally consistent with phenotypic findings of Turner syndrome. *J Clin Exp Invest 2014; 5 (3): 444-448*

Key words: Turner syndrome, 45,X/46,XY, 46,X,i(Xq), mosaisizm

ÖZET

Bu çalışmada Turner sendromunun nadir görülen tiplerinden 45,X/46,X,i(Xq) ve 46,X,i(Xq) karyotipli iki olgunun sitogenetik ve klinik bulguları değerlendirilmiştir. Kadın Doğum ve Hastalıkları Kliniğinden kromozomal anomali endikasyonu ile Sitogenetik Laboratuvarına yönlendirilen iki hastadan alınan periferik kan örnekleri ile Giemsa-Tripsin Bantama yöntemi ile karyotipik inceleme yapıldı.

Olgu 1. Hasta 17 yaşında, kısa boy, düşük saç çizgisi, kısa boyun, göğüsler küçük ve aralıklı, dış genitaller normal ancak iç genitallerde gelişme geriliği var. Hasta 45,X/46,X,i(Xq) karyotipindedir.

Olgu 2. Hasta 19 yaşında, primer amenore, kısa boy, düşük saç çizgisi, göğüsler aralıklı ve az gelişmiş. Dış genitaller normal ancak rahim az gelişmiş, yumurtalıklar belirsiz. Hasta 46,X,i(Xq) karyotipindedir.

45,X/46,X,i(Xq) ve 46,X,i(Xq) karyotipli olgularımızın Turner sendromunun fenotipik bulgularıyla genel olarak örtüşmekle beraber semptom ve belirtilerin daha hafif seyrettiğini söyleyebiliriz.

Anahtar kelimeler: Turner sendromu, 46,X,i(Xq), mosaisizm

INTRODUCTION

The diagnosis of Turner syndrome (TS) is based on the characteristics described by Otto Ullrich and Henry Turner, such as short stature, gonadal dysgenesis (streak gonads), typical dysmorphic features, and abnormalities in organs such as the kidneys and heart. It may be defined as the combination of phenotypic features and complete or partial absence of one of the X chromosomes, frequently accompanied by cell line mosaicism [1]. The symptoms of Turner's syndrome vary a great deal. The most pronounced characteristics of a Turner's patient are her short stature (less than five feet tall) and her failure to mature sexually. Other symptoms may include heart defects, kidney abnormalities, infertility, thyroid dysfunctions, a webbed neck, a low posterior hair line, a broad chest, a small mandible, and prominent ears. Although mental retardation is found in about six percent of the patients with

[1] *Mersin University Medical Faculty Department of Medical Biology and Genetics Mersin, Turkey*
[2] *Mersin University Medical Faculty Department of Gynecology Mersin, Turkey*

Correspondence: Etem Akbaş,
Mersin University Medical Faculty Department of Medical Biology and Genetics, Mersin, Turkey Email: etem_a@yahoo.com

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Turner's syndrome, the majority of Turner's patients exhibit a normal mental capacity with only a small deficit in space-form perception and visual-motor skills [2]. The 45,X cell line arises from meiotic nondisjunction or anaphase lagging during spermatogenesis or oogenesis or from postzygotic error. Clinical manifestations vary and may be subtle; they usually include short stature, webbed neck, broad chest with widely spaced nipples, cubitus valgus, congenital lymphedema, lack of spontaneous pubertal development resulting from ovarian sex hormone insufficiency, a low-posterior hairline, misshapen or rotated ears, narrow palate with crowded teeth, hyperconvex nails, multipigmented nevi, and cardiac malformation [3].

TS incidence is around 1 in 5000 newborn females, even though 97% of the TS conceptions are spontaneously aborted [4]. On chromosomal analysis, the percentage occurrence of the various karyotypes observed in TS are: 45,X (50%), 45,X/46,XX (20%), 46,X,i(Xq)(15%), 46,X,r(X) or 46,X,del(X)(10%) and others (5%).5 Sybert and McCauley observed that: 46,X,i(Xq) (7%), 45,X/46,X,i(Xq) (8%), 45,X/46,X,+ring (6%), 45,X/46,X,+mar (1%), 45,X/46,XY or 46,X,Y/Ydel (7%), 45,X/46,XX/47,XXX (3%), 45,X/46,XX (13%), 46,X,Xp (short-arm deletions) (2%), 46,X,Xq (interstitial long-arm deletions) (2%) and other (6%) [6].

The isochromosome of the long arm of the X chromosome, i (Xq), is the most common structural aberration found in patients with Turner syndrome [7]. Although the classical definition of an isochromosome implies a single functional centromere separating two arms which are mirror images of one another, this term has been used to designate a broader group of chromosome rearrangements, including isodicentrics and duplications of genetically non-identical arms [8]. Mosaicism is the presence of two or more cell lines with different chromosomal constitutions in the affected individuals. The cell lines mostly are derived due to post zygotic mitotic non disjunction and for example represented as 45,X/47,XXX/46,XX/46,XY. The number of the cell lines or the percentage may be given in bracket and the normal diploid karyotype is written last [7]. The chromosome constitution is also clinically significant in this syndrome. Patients with i(Xq) are like classical 45,X patients, whereas patients with a deletion of Xp have short stature and congenital malformations and those with a deletion of Xq have often only gonadal dysfunction [8]. In this study, cytogenetic and clinic findings of 46,X,i(Xq) and 45,X/46,X,i(Xq) which are the rare types of Turner syndrome are evaluated.

METHODS

Cytogenetic studies

After obtaining information regarding her anamnesis and a detailed pedigree analysis, a blood sample was obtained for cytogenetic studies. Giemsa-trypsin banding and karyotyping of prepared lymphocyte cultures were performed according to ISCN 1995 [9, 10]. When metaphases were examined, it was found out that 45,X/46,Xi(Xq) and 46,X,I (Xq) chromosomal structure, and it was reported. Chromosome analysis of hers parents was carried out, using GTG technique. Their parents had normal karyotypes.

CLINICAL PRESENTATION

Case 1

The patient was referred to our clinic with the complaint of primer amenorrhea. She was 17 years old and never menstruated before. Her previous history was unremarkable except recent diagnosis of minimal strabismus. As a child she has always been shorter than his classmates, but the growth retardation became more obvious after 12 years of age. Mental development is not impaired. She presents some of the Turner stigma (Figure 1). Her breasts were small and were assessed to be at Tanner 2-3. Pubic and axillary hair development was minimal. External genitalia appeared to be normal but she could not tolerate bimanual examination. Transabdominal ultrasonography revealed a hypoplastic uterus with the dimensions of 33x23x13 mm.

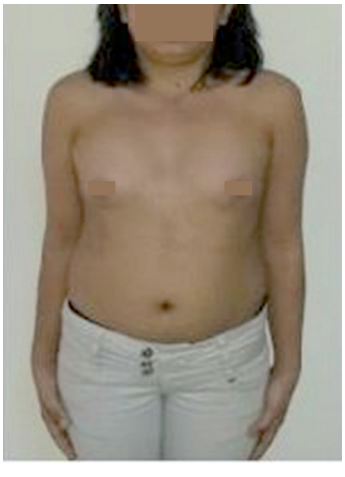

Figure 1. Short stature (height 136 cm and weight 44 kg at 17 years of age), low posterior hair line, short neck, broad chest, widely spaced nipples, hypo plastic nails.

Figure 2a, 2b. Karyotype of the patient

A suspicious thin endometrial lining could be visualized. Adnexa were free of mass and no distinct ovaries could be demonstrated by ultrasonography. Hormonal assessment revealed hypergonadotropic amenorrhea with the results of FSH levels 123 mIU/ml and estradiol levels <10 pg/ml. Because of her primer amenorrhea history, stigma which favors Turner syndrome and unable to visualize the ovaries, chromosomal analyses were evaluated. Her karyotype was 45,X(68%)/46,X,i(Xq) (32%) (Figure 2a,2b).

Case 2

A nineteen years old female presented to our clinic with complaint of primary amenorrhea. She was born to a non-consanguineous couple. School performance and mental capacity wasn't impaired. Family history was uneventful. She was 140 cm tall and weighed 60 kg. Upon physical examination a cluster of signs associated with Turner Syndrome; low hair line, low set ears, broad chest, widely spaced nipples, hypoplastic breast assessed to be at Tanner 2 (Figure 3), sparse axillary and pubic hair were observed. Labia major and vaginal depth was found to be normal. Transabdominal ultrasound scan carried out on patient showed a significantly undersized uterus with the dimensions of 2.5 x 1 x 3 cm. Ovaries weren't visualized. On magnetic resonance imaging uterus was noticeably below the usual size, endometrium was thin and vaginal width was normal. Ovaries weren't visualized. There were any mass and enlarged lymph nodes in pelvic region. Hypergonadotropism was found on laboratory assessments with FSH level of 50 IU/L and estradiol 9.59 pg/mL. Hypothyroidism was also revealed with TSH level of 244.63 µIU/mL. The patient is suspected of Turner Syndrome as findings on physical examination, imaging studies and laboratory tests; as well as the initial complaint favor the diagnosis therefore chromosomal analysis was carried out to confirm. Her karyotype was 46,X,i(Xq) (Figure 4).

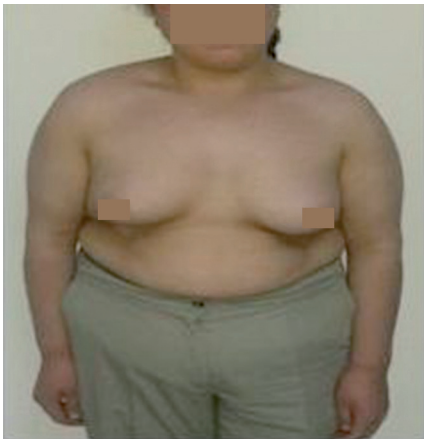

Figure 3. Photograph of patient 2. Low hair line, low set ears, broad chest, widely spaced nipples, hypo plastic breast

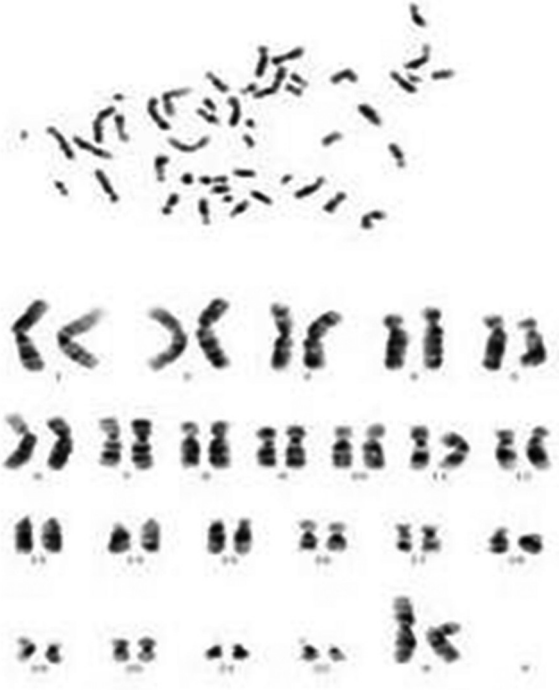

Figure 4. GTG-Banded karyotype 46,X,i(Xq)

DISCUSSION

Case 1 is 17 years old, has short height, a low-posterior hairline, short neck, small and wide apart

breasts, normal external genitals and underdeveloped internal genitals. It is determined in cytogenetic analysis that the patient has 45,X/46,Xi(Xq) mosaic karyotype. Mosaisizm degrease was 45,X(68%)/46,Xi(Xq)(32%) . We compared our mosaic patients with literature. Sybert and McCauley6 observed occurrences of 45,X/46,X,i(Xq) (8%); Gicquel et al. had reported the frequency of 45,X/46,XXi(Xq) karyotype TS as 8,2% respectively [11]. 45,X/46,Xi(Xq) mosaic karyotype are rare types of Turner syndrome as shown in 6th and 11th literature findings. Kuznetzova et al had reported a case with 45,X146,X, i(Xq). Clinical features: Short stature, arched palate, short neck, shield chest, cubitus valgus, external genitalia hypoplasia. Gonads not detected and streak uterus [12]. The clinical findings of our case and clinical findings of Kuznetsova's group's case are mostly consistent. Jelic and Marisavlievic had reported an 18-year old patient with TS with mosaic karyotype 45,X/46,X,i(Xq) and renovascular hypertension is presented13. There is not renovascuar hypertension in our case yet. Mühlenstedt at all had reported an 22 years old patient with TS with mosaic karyotype 45,X/46,X,i(Xq). Who had a gonodoblastoma with overgrowing dysgerminoma [14]. There was no gonodoblastoma in our case yet.

Case 2 is 19 years old, has primer amenore, short height, a low-posterior hairline, wide apart and underdeveloped breasts, normal external genitals, underdeveloped uterus, obscure ovarium. It is determined in cytogenetic analysis that the patient has 46,X,i(Xq) karyotype. We compared the characteristics of the patient with46,X,i(Xq) karyotype with the characteristics of other cases with that karyotype reported in the literature. Kuznetzova et al had reported two cases with 46,X,i(Xq) karyotype.12 Case 1: Clinical features: Short stature, arched palate, short neck, cubitus valgus, external genitalia hypoplasia and streak uterus. Case 2: Clinical features: Short stature, epicanthic folds, Thyroid gland hypertrophy, and external genitalia hypoplasia. The cases of Kuznetzova et al have external genitalia hypoplasia, while our cases have normal external genitalia. Other findings are mostly consistent. Liu at al. history of a variant type of TS (46,XXqi) with type 2 diabetes mellitus under insulin therapy for more than 10 years. She had been admitted because of diabetic retinopathy and cataract. Her uremic symptoms developed after progressive deterioration of her renal function. There is no diabetes mellitus disease and its side effects in our case. Akbaş at all reported that a case with 46,X,i(Xq) karyotype. She had 10 years old girl. Physical examination revealed her height to be 119 cm and her weight to be 29 kg. Clinical features: She had edema of the hands and feet, short hands and fingers, and a low -posterior hairline. Results of the examination of her external genitalia appeared to indicate labial synechiae. Abdominal ultrasonic imaging revealed a horseshoe kidney. Her short stature was treated with medical therapy by a pediatric endocrinologist; her height increased to 132 cm in the following 15 months [15]. Balkan at all reported that a case with 46,X,i(Xq) karyotype. She had 14 years old girl having complaints of growth retardations and primary amenorrhea. In the physical and gynecological examinations; her height and weight were 130 cm and 45 kg, respectively and secondary sex characteristics were infantile and hymen annular was intact and the depth of vagina was 7 cm and, palpitate of pelvis was empty. The case did not show broad chest, neck webbing and low posterior hairline. Uterus dimensions were 11x7x4 mm and ovaries were not seen in ultrasonographic examination [16]. Clinical findings of our case are mostly consistent with [15] and [16].

The 46,X,i(Xq) karyotype is found in 7% to 16.7% of individuals with TS.4,16 Patients with i(Xq) have similar characteristics to those with classical 45,X; however, patients with a deletion of Xp have short stature and congenital malformations. Those with deletion of Xq often only have gonadal dysfunction [17]. Some reports [18,19] have indicated that patients with the 46,X,i(Xq) karyotype have characteristics similar to those observed in classical TS. Those reports claim that the risks for hypothyroidism and mild mental retardation are higher in these patients than in the healthy population. Comparing the individual with isochromosome Xq with individuals who have the 45,X type of TS, the probability of partially developed nipples and mental retardation was higher but the probability of a low-posterior hairline, neck webbing, and hypoplastic nails was lower [20]. Liu at all reported that 48-year-old Chinese woman had a history of a variant type of TS (46,XXqi) with type 2 diabetes mellitus under insulin therapy for more than 10 years. She had been admitted because of diabetic retinopathy and cataract at the age of 39. Because uremic symptoms developed after progressive deterioration of her renal function, she decided to receive renal replacement therapy at the age of 44 [21].

Clinical symptoms of our patients that have mosaism (68% 45,X, 32% 46,X, i(Xq) karyotype) and clinical symptoms of our patients that have 46,X,i(Xq) karyotype are slightly weaker than Turner syndrome. Considering patients' ages, height

development is better, primer and secondary gender characteristics (development of internal and external genitals) are not as weak as in Turner syndrome. However, the clinical course is milder in our patients. Because physical examination, electrocardiographic readings, and chest X-ray examinations did not reveal heart disease or cardiac abnormalities, we did not perform detailed evaluations of cardiac function. These cases contribute to the literature detailing the clinical symptoms.

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