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Late Diagnosis of Turner Syndrome: Isochromosome X, about Five Cases.

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ABSTRACT: Background: Turner syndrome is diagnosed by combining certain phenotypic characteristics with the absence of an X chromosome. This absence may be total or partial, such as occurs with X isochromosomes. The phenotypic consequences of these depend on 2 factors: the nature of the genes that have been lost and the percentage of 45, X cells in the mosaicism.

The clinic changes according to the cytogenetic pattern, with short size prevailing as a phenotypic manifestation, since it lies in the haplo- insufficiency of the SHOX gene on the short arm of the X chromosome. Thus, when there are long arm isochromosomes, short stature is always present. However, typical features may be absent, leading to diagnostic delay.

Methods: This was a retrospective study of five patients with suspected TS evaluated the same clinical and cytogenetic protocols. Data regarding reason for referral, age and height at diagnosis, birth data, pubertal features and dysmorphisms were analyzed.

Results: TS was diagnosed in all the five patients. Primary amenorrhea was the main reason for referral of patients. The cytogenetic analysis showed an X isochromosome either in a homogeneous or mosaic formula.

Conclusions: Though short stature, pubertal delay and typical stigmata should prompt investigation of TS, lack of one of these features should not exclude this hypothesis.

KEYWORDS: Turner syndrome, Isochromosome X, Primary amenorrhea, karyotype.

I. INTRODUCTION

Turner syndrome is diagnosed by combining certain phenotypic characteristics with the absence of an X chromosome, which may be partial like that which occurs in X isochromosomes. It is the most frequent isochromosomopathy in humans, so the karyotype in peripheral blood must be one of the first steps in the diagnosis. The clinical picture may vary depending on the cytogenetic pattern, with short stature prevailing as the most frequent phenotypic manifestation, usually with disproportion between the upper and lower hemi-body. Others are the manifestations derived from primary hypogonadism, which appear in the pubertal stage. However, typical features may be absent, sometimes leading to a delay in diagnosis[1].

We present five cases of late diagnosis of Turner syndrome given the scarce phenotypic manifestations, all with cytogenetic diagnosis of X isochromosome.

II. CASES REPORTS

CASE 1:

A 27-year-old female of no consanguineous parents was sent to our Medical Biology and Genetics laboratory for karyotype analysis for clinical findings of short stature and primary amenorrhea. Her birth weight and length were

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unknown. On physical examination, she was found to be 137 cm tall, weighing 30 kg, with body mass index (BMI) of 16 kg/m². Clinical findings included decreased secondary sex characteristics with: Breast development in Tanner stage I, pubic hairs in Tanner stage II, axillary hairs absent, and infant vulva. Low set ears and low posterior hairline was observed. On ultrasound, she had a Hypoplastic uterus and small ovaries. She had the following laboratory work-up that included hormone testing: follicle-stimulating hormone: 67.46 mIU/ mL, luteinizing hormone: 4.68 mIU/mL, thyroid-stimulating hormone (TSH): 1.2 μ IU/mL, estradiol (E2): < 10 pg/mL. Her IQ score was with a normal distribution.

CASE 2:

A 20-year-old female of no consanguineous parents was sent to our Medical Biology and Genetics laboratory for karyotype analysis for clinical findings of primary amenorrhea. Her birth weight and length were unknown. On physical examination, she was found to be 145 cm tall, weighing 44 kg, with body mass index (BMI) of 20.95 kg/m². Clinical findings included decreased secondary sex characteristics with: Breast development in Tanner stage III, pubic hairs in Tanner stage II, axillary hairs present and infant vulva. Low set ears were observed. On ultrasound, she had a Hypoplastic uterus and small ovaries. She had the following laboratory work-up that included hormone testing: follicle-stimulating hormone: 86.28 mIU/ mL, luteinizing hormone: 26.64 mIU/mL, thyroid-stimulating hormone (TSH): 2.21 μ IU/mL, estradiol (E2): < 10 pg/mL. Her IQ score was with a normal distribution.

CASE 3:

A 16-year-old female of no consanguineous parents was sent to our Medical Biology and Genetics laboratory for karyotype analysis for clinical findings of oligomenorrhea. Her birth weight and length were unknown. On physical examination, she was found to be 138 cm tall, weighing 38 kg, with body mass index (BMI) of 20 kg/m². Clinical findings included decreased secondary sex characteristics with: Breast development in Tanner stage IV, axillary hairs in Tanner stage III and Pubic hairs in Tanner stage IV. On ultrasound, she had a Hypoplastic uterus. She had the following laboratory work-up that included hormone testing: follicle-stimulating hormone: 94.99 mIU/ mL, luteinizing hormone: 24 mIU/mL, thyroid-stimulating hormone (TSH): 1.2 μ IU/mL, estradiol (E2): < 10 pg/mL. Her IQ score was with a normal distribution.

CASE 4:

A 17-year-old female of no consanguineous parents was sent to our Medical Biology and Genetics laboratory for karyotype analysis for clinical findings of primary amenorrhea. Her birth weight and length were unknown. On physical examination, she was found to be 138 cm tall, weighing 43.8 kg, with body mass index (BMI) of 23 kg/m². Clinical findings included decreased secondary sex characteristics with: Breast development in Tanner stage I, pubic hairs in Tanner stage II, axillary hairs absent and infant vulva. Low set ears, Webbed neck, Cubitus vulgus and Short fourth metacarpals were observed. On ultrasound, she had a Hypoplastic uterus, small ovaries and renal malformation. She had the following laboratory work-up that included hormone testing: follicle-stimulating hormone: >150 mIU/ mL, luteinizing hormone: 19.26 mIU/mL, thyroid-stimulating hormone (TSH): 0.91 μ IU/mL, estradiol (E2): < 10 pg/mL. Her IQ score was with a normal distribution.

CASE 5:

A 21-year-old female of no consanguineous parents was sent to our Medical Biology and Genetics laboratory for karyotype analysis for clinical findings of primary amenorrhea. Her birth weight and length were unknown. On physical examination, she was found to be 144 cm tall, weighing 45 kg, with body mass index (BMI) of 21.7 kg/m². Clinical findings included decreased secondary sex characteristics with: Breast development in Tanner stage III, slight axillary hairs and pubic hairs, and shield chest. On ultrasound, she had a Hypoplastic uterus and small ovaries. She had the following laboratory work-up that included hormone testing: follicle-stimulating hormone: 90.28 mIU/ mL, luteinizing hormone: 25.64 mIU/mL, thyroid-stimulating hormone (TSH): 1.6 μ IU/mL, estradiol (E2): < 10 pg/mL. Her IQ score was with a normal distribution.

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Clinical Detail	CASE 1	CASE 2	CASE 3	CASE 4	CASE 5
Age (In Years)	27	20	16	17	21
Consanguinity	-	-	-	-	-
Height (In Cm)	137	145	138	138	144
Weight (In Kg)	30	44	38	43,8	45
BMI (IN Kg/M2)	16	20,95	20	23	21.7
Growth Retardation	+	-	-	-	-
Menstrual Status	Primary amenorrhoea	Primary amenorrhoea	Oligo-amenorrhoea	Primary amenorrhoea	Primary amenorrhoea
Mental Retardation	-	-	-	-	-
Lymphedema	-	-	-	-	-
Webbed Neck	-	-	-	+	-
Low Set Ears	+	+	-	+	-
Cubitus Vulgus	+	-	-	+	-
Short Fourth Metacarpals	-	-	-	+	-
Cardiovascular Abnormality	-	-	-	-	-
Autoimmune Disorder	-	-	-	-	-
High Arched Palate	+	-	-	-	-
TSH (μ IU/ml)	1,2	2,21	1,2	0,91	1.6
FSH (mIU/ml)	67,46	86,28	94,99	>150	90.28
LH (mIU/ml)	4,68	26,64	24	19,26	25.64
E2 (pg/ml)	<10	<10	<10	<10	<10
Development of Secondary Sexual Characters	Breast Development—Tanner Stage I Pubic Hairs—Tanner Stage II Axillary Hairs Absent, And Infant Vulva	Breast Development—Tanner Stage III, Pubic Hairs—Tanner Stage II Axillary Hairs Present, And Infant Vulva	Breast Development—Tanner Stage IV, Axillary Hairs—Tanner Stage III and Pubic Hairs—Tanner Stage IV	Breast Development—Tanner Stage I, Pubic Hairs—Tanner Stage II Axillary Hairs Absent, And Infant Vulva	Breast Development—Tanner Stage III, Slight Axillary Hairs and Pubic Hairs, And Shield Chest
Renal Malformation	-	-	-	+	-
Ultrasonographic Report	hypoplastic uterus and small ovaries	hypoplastic uterus and small ovaries	hypoplastic uterus	hypoplastic uterus and small ovaries	hypoplastic uterus and small ovaries
Neurocognitive Phenotype	-	-	-	-	-

Table 1 : Comparative clinical features of the five cases

III. RESULT

Based on the patient's findings, the clinical diagnosis of Turner Syndrome was highly suspected, and a metaphysical karyotype was performed in all patients.

The results of the karyotype analysis are in the following table: Table 2, Figure 1

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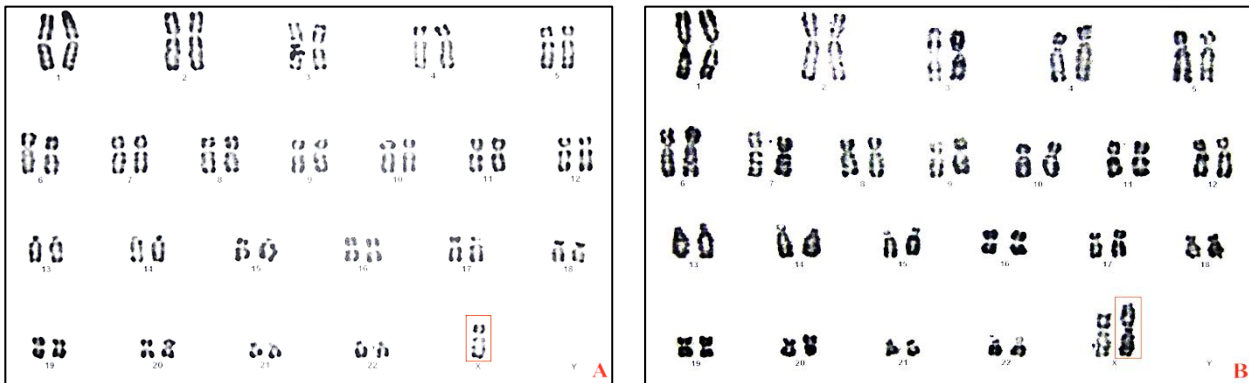


Fig1: Cytogenetic analysis showing the (A) first cell line with loss of one X chromosome, resulting in monosomy X, while (B) the second cell line with an isochromosome of the long arm of X chromosome.

Case ID	Cell types	Mosaicism for 46,X,i(X)(q10)
Case 1	46,X,i(X)(q10)	100%
Case 2	46,X,i(X)(q10)	100%
Case 3	45,X/46,X,i(X)(q10)	35%
Case 4	45,X/46,X,i(X)(q10)	55%
Case 5	45,X/46,X,i(X)(q10)	25%

Table 2: Comparative cytogenetic description of five cases.

IV. DISCUSSION

The clinical diagnosis of Turner syndrome is highly variable depending on the stage of life in which it is determined. In the prenatal period, generalized nuchal cystic hygroma can be observed, in the neonatal, lymphedema and in childhood, low height. In adolescents, it can be diagnosed as a result of pubertal retardation or primary amenorrhea.

Turner syndrome is known to cause short stature by loss of critical length-related genes on the X chromosome. Short stature present in 100% of cases is the starting point for diagnosis as it is sometimes the only symptom. However, the final size is usually related to the average parental size, so those patients who are in percentiles above the p50 of the population will be those who have greater diagnostic delay, especially if other phenotypic manifestations are not observed.

Some patients will therefore not be diagnosed until the onset of puberty, where the lost growth potential will be greater, since they will not yet have received treatment with GH, depriving them of the final size gain it brings.

The factors that most influence the results of GH treatment are age of onset, duration of treatment and the dose received before oestrogenisation, so early diagnosis is a primary goal of the clinician.

The initiation of growth hormone therapy should be indicated at the time when the height of the Turner syndrome patient is below the 5th percentile in relation to her age, which usually occurs between 2-5 years[2]. Furthermore, the beginning of treatment improves the body composition, increasing the lean mass and decreasing the fat mass[3].

In fact, early initiation of growth hormone therapy in girls with Turner syndrome has been shown to improve and even normalize final height in some cases [4–7]. Similarly, late initiation of this treatment in patients aged 10-13

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years leads to an increase in height of between 2.1 and 7 cm with respect to untreated controls[8,9], so the benefit remains favorable but less so.

More than a third of Turner syndrome patients have some degree of mosaicism [10–12]. The genotypic identification of Turner syndrome depends directly on the method used for its diagnosis, ranging from 34% with conventional cytogenetic techniques to 60% with fluorescence in situ hybridization techniques[13]. Classically, the presence of X isochromosomes is associated with the absence of congenital abnormalities, and with a high rate of auto-immune diseases (Crohn's disease, lymphocytic thyroiditis) and deafness, which could lead to a delay in diagnosis as in the cases presented[14,15]. The phenotypic consequences of these isochromosomes depend on 2 factors: the nature of the genes that have been lost and the percentage of 45,X cells; likewise, they are practically never found forming mosaics with normal XY populations, which translates the fact that the chromosomal abnormality has its origin in parental meiosis[16,17].

In any case, the short size of Turner syndrome lies in the haploinsufficiency of the SHOX gene on the short arm of the X chromosome. Therefore, when there are isochromosomes of the long arms of the X chromosome, the short size is a common finding[18–20]. Other phenotypic findings related to genetic haplotyping in patients with Xq isochromosome are the alteration of lymphogenic genes, and their craniofacial and cervical manifestation by compression of the lymphatic system. Other manifestations in relation to this lymphogenic alteration would be the presence of short metacarpals, ulna valgus or micrognathia, although they occur in a lower proportion than in patients with monosomy X[19,20].

All five of our patients have few phenotypic manifestations of Turner syndrome, so this could lead to a deferral of diagnostic suspicion to later age.

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