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CASE REPORT OPEN ACCESS

ISOCHROMOSOME MOSAIC TURNER SYNDROME WITH DELAYED GROWTH AND PUBERTY: A CASE REPORT

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Abstract

Isochromosome Mosaic Turner Syndrome, a variant of Turner syndrome which has a milder presentation, can present without the typical features of Turner syndrome. Evaluation of Turner syndrome with karyotyping has to be performed in females presenting with short stature. We present a case of 15 years girl who presented with delayed growth and puberty with primary amenorrhea and hyperthyroidism. Cytogenetic study of peripheral blood revealed 45,X [31]; 46, X,i(X)(q10) [19] suggestive of Isochromosome Mosaic Turner Syndrome.

Key Words: Isochromosome, Grave's disease, short stature, Turner syndrome

Introduction

Turner syndrome (TS) is characterized by the loss of all or part of a normal second X chromosome; monosomy X (45, X) being the most common karyotype.[1] Isochromosome Mosaic Turner Syndrome (IMTS) is characterized by the presence of isochromosome in addition to 45,X.[2] Around 45% of cases of TS are due to non-mosaic monosomy of chromosome X and about 10-35% of cases are due to X chromosome rearrangements like isochromosome Xq.[3] 46,X,i(Xq) karyotype usually presents with short stature due to SHOX haploinsufficiency.[2] Mosaic Turner syndrome has the least severe phenotype and spontaneous puberty with menstruation occurs in up to 40% of cases.[4]

This report is a case of 15 years old girl with IMTS who presents with delayed growth and puberty. It emphasized that karyotyping is of utmost importance in a girl who presents with short stature as one-third of girls diagnosed with TS in mid-childhood on the investigation of short stature.[1]

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Case report

A 15 years girl accompanied by her mother presented to our hospital with short stature, delayed secondary sexual characteristics, and significant weight loss. Her menarche had not started and the breasts and nipples were not developed for her age. Both of her parents had normal height. Neither there was a history of delayed growth nor there was a history of delayed puberty in family members. She had no chronic illness and recurrent hospitalizations in the past. She had significant weight loss associated with anterior neck swelling, tremors, sweating, and palpitation. She was born from a non-consanguineous marriage. Her birth history was uneventful and her developmental milestones were appropriate for her age. She had normal intelligence.

On examination, she was under-weight with a BMI of 16.70 kg/m2. She was anxious and tachycardic. There were no dysmorphic features as well as features of Turner syndrome. She had Tanner stage [2] breast (figure 1) and pubic hair development. She

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had proportionate short stature with a height of 134 cm which was below the 3rd percentile. Her mid-parental height was 151 cm and her arm span was 134 cm. There was the presence of diffuse symmetrical goiter with a rubbery firm consistency. Her systemic examinations and otorhinolaryngology examination were unremarkable.

On investigation, she was found to be thyrotoxic [TSH: <0.015µIU/mL (0.46-4.68), fT4: >6.99ng/dL (0.78-2.19), fT3: >22.8 pg/mL (2.77-5.27)]. She had hypergonadotropic hypogonadism [FSH: 66.3 IU/mL, LH: 18.3 mIU/mL, Estradiol: 14.12 pg/mL]. Her prolactin level was elevated (36.3ng/mL). MRI abdomen and pelvis revealed a hypoplastic uterus with non-visualized ovaries and a normal vaginal canal. MRI brain and echocardiography were normal. A radiograph of the left wrist revealed non-fusion of epiphyseal plates with delayed bone aging for females for her age (figure 2). Cytogenetic study of peripheral blood showed two cell lines. The karyotype revealed 45, X [31]; 46, X, i(X)(q10) [19] suggestive of isochromosome mosaic turner syndrome. Her mother was counseled regarding the treatment with growth hormone. However, growth hormone was not started due to financial constraints. The benefits and risks of initiation of estrogen therapy were discussed.

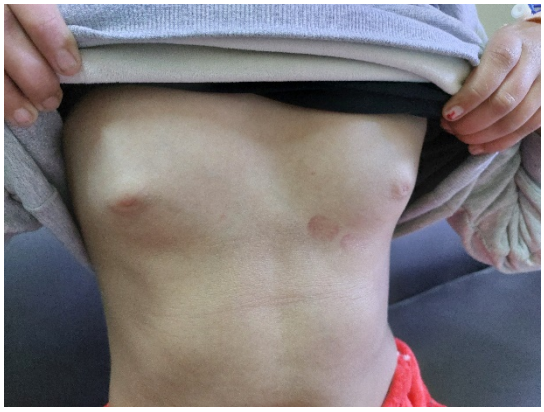

Figure 1. Tanner stage 2 breast development

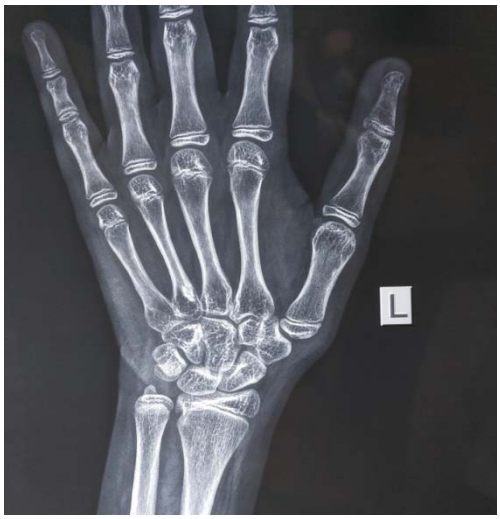

Figure 2. Radiograph of the left wrist showing delayed bone age with non-fusion of epiphyseal plates

Discussion

Turner syndrome is named after Henry Turner who described its phenotypic features and is characterized by either monosomy of X chromosome or mosaicism of 45X cell line with another cell line. Short stature and gonadal dysgenesis are consistent clinical features and the severity of the clinical phenotype is usually dependent upon cytogenetics.[4] Turner syndrome occurs in 1: 2500- 3000 live births; the isochromosome of the long arm of the X chromosome is the most common structural alteration accounting for 10-23%.[5] Mosaicism results in the development of two cell lines of different genetic makeup due to the non-disjunction of sex chromosomes during either mitosis or meiosis which results in different phenotypes.[6] 46,X,i(Xq) karyotype was found in 8 % of patients with TS according to Sybert and McCauley.[1] Akbas E. et al.[7] reported two patients (12%) had 46,X,i(Xq) karyotypes when 17 of 1681 patients were investigated with cytogenetic evaluation for the uncertain chromosomal anomaly. Isochromosome X [46,X,i(X)], Ring Chromosome [46,X,r(X)], Deletion (Xp or Xq) are different

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structural abnormalities of X chromosome associated with TS.[2]

Turner syndrome is either diagnosed during the neonatal period due to the presence of puffy extremities or redundant nuchal skin, or either diagnosed during the mid-childhood while investigating short stature. Likewise, the syndrome is diagnosed during adolescence due to delayed puberty. Evaluation for Turner syndrome has to be done in a short-stature girl with primary or secondary amenorrhea.[1] The 46,X,i(Xq) karyotype may have clinical characteristics similar to classical TS; however, the risk of hypothyroidism, underdeveloped nipples, and mild mental retardation is higher than in the healthy population.[7] The 45,X/46,X,i(Xq) karyotype TS patients usually present with cardiac disease with structural malformations, renal malformations, menstrual disorders, short stature, and mental retardation.[1] Akbas E. et al.[7] reported two cases of 46, X, i(Xq) karyotype with short stature, one case of 10 years old girl who also had edema of hands and feet, short hands and fingers, and a low posterior hairline, however, her bone age was not delayed with epiphyseal development appropriate for her age. The other case was of 24 years and presented with secondary amenorrhea. They found that the isochromosome i(Xq) form of TS was generally milder than classic TS. In another case report, a 20 years old isochromosome mosaic turner syndrome had short stature and primary amenorrhea with non-visualized ovaries and infantile uterus. There were delayed secondary sexual characteristics with Tanner stage I pubic hair and breast development and non-fusion of epiphyseal plates with bone aging for females of 13 years old. She was screened for complications, however, her echocardiography, audiogram, and ultrasound abdomen revealed normal findings.[8] Short stature is usually a presentation in TS, with adult height approximately 20 cm shorter than controls of the same ethnicity. The haploinsufficiency of the SHOX gene, located in the pseudo-autosomal region of Y and Xp, leads to premature growth plate fusion leading to short stature and other skeletal features of TS, like cubitus valgus, high arched palate, micrognathia, and Madelung deformity.[1, 9]

Gonadal dysgenesis occurs in TS with no pubertal development in 85%, infertility in 98%, and chronic estrogen deficiency in 95-98% of patients.[9] The chromosomal aberration causes either complete or partial gonadal dysgenesis causing hypergonadotropic hypogonadism which would require hormone replacement therapy for initiation of puberty. The germ cells develop normally however there is progressive and expedited loss of oocytes which results in delayed or absent puberty.[10] Turner syndrome is associated with autoimmune hypothyroid disease in patients with an isochromosome of the long arm of the X chromosome (i(Xq)), and as many as 30% or more eventually develop hypothyroidism.[9] A study done in Italy in 66 cases with Turner syndrome showed an increased frequency of thyroid autoimmune disorders, however, none of these patients had Grave's disease.[11] The association of TS with Grave's disease is not frequent however there are few reports.[12-14] Zhang et al.[13] reported a gene karyotype of 46,X,i (X)(q10) in a 16-year-old girl with TS. Turner syndrome is associated with retarded bone age from the chronological age of 3 to 6y.[15] Estrogen deficiency in TS may be the cause of such delayed epiphyseal closure.[16]

Treatment of Turner syndrome with recombinant growth hormone was FDA approved in 1997, however, it is very expensive, and ideal dosing and duration of treatment are not well established.[1] A study done in India in 16 cases of TS who were treated with human recombinant GH at the dose of 0.3 mg/kg/week administered as daily subcutaneous injections showed an increase in height from 1.26 to 1.37 m achieved with a mean duration of 25 months of GH therapy.[17] Estrogen therapy can be used for the induction of puberty. There is concern regarding the early epiphyseal closure and the limitation of longitudinal growth. However, low dose Ethinyl estradiol can be used since there is no significant

detrimental effect on final height with the use of estradiol treatment.[18]

Conclusion

The clinical features in IMTS are milder than 45,X0 Turner syndrome. In our case, the patient presented with delayed growth and puberty, and hyperthyroidism. IMTS has not been reported earlier in Nepal. Turner syndrome has to be evaluated with cytogenetic analysis in a female child who presents with short stature without typical features so that management can be initiated earlier.

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