RARE ASSOCIATION BETWEEN TWO GENETIC CONDITIONS: TURNER SYNDROME AND BETA THALASSEMIA MINOR

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Abstract: Rare disorders are defined as diseases, including those of genetic origin, which are life-threatening or chronically debilitating, which are of such low prevalence that special combined efforts are needed to address them. We present a case with a rare association between two genetic conditions: Turner phenotype and beta thalassemia minor. Turner syndrome is a chromosomal disorder that is characterized by the absence of all or part of a second sex chromosome in some or all cells. This condition occurs in 1 in 2,500 to 3,000 girls. The physical features include webbing of the neck, short stature, delayed growth of the skeleton, broad chest, cardivascular abnormalities and gonadal dysgenesis. Women with this disorder are usually infertile due to ovarian failure. The clinical diagnosis was confirmed by the cytogenetic and by FISH analysis, which revealed the presence of only one X chromosome. Treatment may include human growth hormone and estrogen replacement therapy. On the other hand, thalassemias are genetic conditions that result from imbalance in the normal coordinated synthesis of the globin subunits that make up the hemoglobin tetramer, leading to decreased and defective production of hemoglobin. Beta thalassemia syndromes are hereditary disorders characterized by a genetic deficiency in the synthesis of beta-globin chains. β thalassemia is inherited in an autosomal recessive manner. Thalassemia minor usually presents as an asymptomatic mild microcytic anemia, but our case also had splenomegaly and required splenectomy.

Keywords: Turner syndrome, β thalassemia minor, rare diseases

INTRODUCTION

Rare disorders are defined as diseases, including those of genetic origin, which are life-threatening or chronically debilitating, which are of such low prevalence that special combined efforts are needed to address them. Genetic disorders are usually considered to be rare diseases, thus for affected individuals and their families, but also for their primary and specialty care physicians, it is essential to recognize them and provide the appropriate treatment and support. Some of these conditions may recur again in families and may cause medical and social problems. Genetic disorders may be caused by changes in the structure or number of the chromosomes or in the DNA.

Turner syndrome is among the most common sex chromosomal aneuploidies, affecting 1/2500 - 1/3000 females. It results as the consequence of the absence of one sex chromosome or part of an X chromosome in a female, with only one normal X chromosome present in the cell. It is estimated that 15/1000 of clinically recognized pregnancies are 45,X and more than 99% do not survive beyond 28 weeks of gestation.

The absence of a normal second sex chromosome leads to a constellation of physical abnormalities, such as short stature, signs of ovarian failure and skeletal dysplasia. The typical findings in Turner syndrome include congenital lymphedema, neck webbing, low posterior hairline, short stature, gonadal dysgenesis and often renal and cardiovascular anomalies. Prematurity is common in pregnancies of infants with the disorder. Growth velocity is less than normal, intrauterine growth retardation and progressive decline in growth velocity during childhood being frequently noticed. Affected females have characteristic craniofacial features, short and broad neck, pterygium coli, shield chest with increased internipple distance, different skeletal manifestations. Congenital heart defects are estimated to occur in about 30% of the cases. Autoimmune diseases, vascular anomalies or genitourinary lesions were also associated with the disorder [1].

Affected subjects have normal female external genitalia, but because they lack functioning ovaries and thus the estrogens produced by ovaries, neither breast development, nor menstruation occurs spontaneously at puberty, primary amenorrhea representing the main reason to seek diagnosis. Progressive ovarian failure and sterility or in some cases infertility are other hallmarks of the disease.

Most individuals with Turner syndrome have normal intellligence. Significantly higher verbal level than performance level attributed to a specific space form-perception deficit was described for many teenagers with this condition [14].

Turner syndrome phenotype is highly variable and there is not a single feature specific only for this syndrome. That is why for the diagnosis of Turner syndrome demonstration of the cytogenetic abnormality is absolutely necessary [12].

The most frequent chromosome constitution in Turner syndrome is 45,X with no second sex chromosome, either X or Y. However, about 50 percent of cases have other karyotypes. About one quarter of Turner syndrome cases involve mosaic karyotypes (45,X/46,XX), the others having deletions of the short or long arm of the X chromosome, but ring chromosomes or isochromosomes may also be seen. Usually the single X is maternal in origin; in other words, the meiotic error is usually paternal.

The number of detectable aberrations has increased to several thousands during the last decades. When a chromosomal abnormality is suspected, cytogenetic analysis is the most common approach used for detection. Methods involving application of conventional banding techniques were initially used,

but advances in molecular cytogenetics, especially the technique of fluorescence in situ hybridization (FISH), have allowed obtaining of more precise information especially on chromosomal structure [6].

Thalassemia refers to a spectrum of diseases characterized by reduced or absent production of one or more globin chains. They are genetic conditions that result from imbalance in the normal coordinated synthesis of the globin subunits that make up the hemoglobin tetramer, leading to the decreased and defective production of hemoglobin. Hemoglobin is a tetramer that consists of 2 pairs of globin chains. There are two hemoglobin gene clusters involved in the production of hemoglobin located at the end of the short arm of chromosomes 16 and 11, respectively. Their control is complex, including an upstream locus control region on each of these chromosomes as well as an X-linked control site [4].

Beta thalassemia syndromes are hereditary disorders characterized by a genetic deficiency in the synthesis of beta-globin chains. Beta thalassemia is inherited in an autosomal recessive manner. Beta-thalassemia minor refers to the heterozygous carrier state for beta-thalassemia. The vast majority of adult cases with beta thalassemia minor are asymptomatic, some may have a normal to slightly reduced hemoglobin level, microcytosis and hypochromia [13].

Thalassemias can now be diagnosed not only by conventional clinical and blood testing, but also using molecular technologies. These tests allow accurate diagnosis to be made [9].

MATERIALS AND METHODS

We report a case with a rare association between Turner phenotype and beta thalassemia minor. The subject, a 22 years old caucasian female presented in our departments for evaluation and counseling. The history of the subject reveals that she is the first child, born from non consanguineous parents. Her medical history revealed that she was diagnosed with β thalassemia minor during childhood, at that time having mild anemia, with hypochromia and microcytosis. Anemia began to develop within the first months after birth. It became progressively more and more severe. She presented recurrent hemolytic episodes and repeated transfusions were needed. Physical examination was initially apparently remarkable only for splenomegaly. Splenectomy was needed, which also decreased transfusion requirements. Growth failure was not diagnosed until midteens, when together with the absence of secondary sex characteristics and primary amenorrhea raised the suspicion of Turner syndrome. Detailed family history was taken and the only remarkable element was that her mother was a silent β thalassemia carrier.

RESULTS

Clinical and functional evaluation of the case revealed:

- Clinical features:
  - Height: 150 cm
  - Webbed neck,
  - Broad chest
  - Widespread nipples
  - Liver: 4 cm under costal margin
  - Hypoplastic nails
  - Lack of secondary sexual characteristics
- Hormonal measurements:
  - Low FSH: 0.7 mUI/ml (may be explained by deposit of iron in hypophyse due to repeted transfusions).

Turner syndrome clinical diagnosis was confirmed by the cytogenetic analysis, which revealed the presence of only one X chromosome (Fig. 1). Chromosomal investigation was performed by conventional G-banding technique, completed by fluorescence insitu hybridization (FISH), which was done on interphase cells and on metaphase chromosomes. Karyotype was 45, X. FISH technique

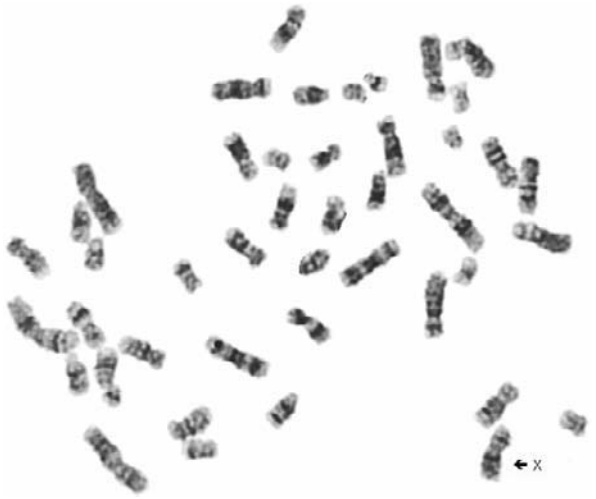

Figure 1. Metaphase revealing 45 chromosomes, with only one X chromosome (100x).

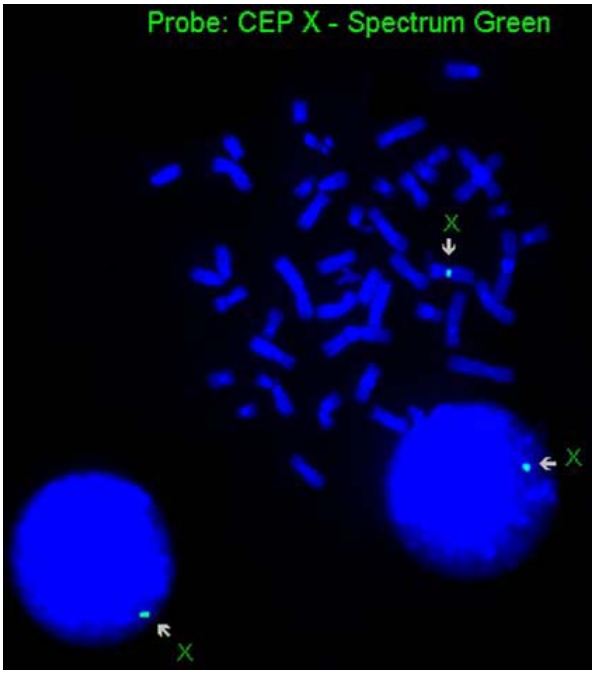

Figure 2. Metaphase and nuclei analyzed by FISH technique using CEP X probe Spectrum Green- Abbott – Vysis, revealing the presence of only one X chromosome (100x).

was performed using CEP X probe Spectrum Green-Abbott - Vysis, and a number of 50 metaphases and 200 nuclei were analyzed, all revealing the presence of only one signal specific for the X chromosome (Fig. 2). This allowed us to consider that the subject has an homogeneous X monosomy.

Treatment may include human growth hormone and estrogen replacement therapy. Estrogen replacement was used to spur growth of secondary sexual characteristics and also for maintaining bone integrity and tissue health.

Thalassemia minor usually presents as an asymptomatic mild microcytic anemia, but our patient also had splenomegaly and required splenectomy.

Cases with Turner syndrome should be referred to cardiology, urology, audiology and endocrinology, because of the possible presence of congenital heart diseases, hypertension, urological problems, sensorineural hearing loss or hypothyroidism as well as for the treatment of gonadal dysgenesis.

DISCUSSIONS

In 1938 Turner reported sexual infantilism, short stature, webbed neck, cubitus valgus and primary amenorrhea, all present in seven female cases [5]. Later in 1954, it was observed that the ovaries were replaced by streaks of stroma without follicles. Only one X chromosome was demonstrated cytogenetically in these subjects in 1959. There is a vigorous prenatal selection against chromosome aberrations. About 99% of 45,X fetuses are aborted spontaneously predominantly during the first 12 weeks of gestation, due to severe dysplasia of the lymphatic system and only 1% of these fetuses survive to term. Despite this, Turner syndrome is a relatively common chromosome disorder. It is estimated that about 10% of all spontaneous abortuses have a 45,X karyotype. Vast majority of Turner syndrome cases lack the paternal sex chromosome, non disjunction in male meiosis I accounting for 80% of cases. This is the only known viable monosomy. In general, abnormalities involving the sex chromosomes are better tolerated than autosomal abnormalities because only one X is active in the normal adults.

At birth Turner syndrome often manifests with extensive edema. The edema in the neck and hands results in neck webbing and arched nails. Turner females are very short, sterile due to gonadal dysgenesis, with primary amenorrhea, broad chests, and usually have heart and kidney defects. In females the lack of one of the X chromosomes can lead to total sterility. It is prudent to rule out mosaicism with Y chromosome material because of the increased risk for gonadal blastoma [3].

Regarding the possible cytogenetic findings it is estimated that 50% of affected females are 45, X., about 25% have structural abnormalities such as isochromosome, ring chromosome or deletions of the p or q arms. About 20% are mosaic: 45,X/46XX; 45,X/abnormal X; or 45,X/47,XXX and 4% of mosaic cases were found to be XY conceptuses who lost the Y in some cells and are: 45,X/46,XY. These females are virilized at birth and at puberty and they have risk of malignancy of the dysgenetic gonad, so it is recommended that the gonads should be removed. There are some controversies regarding the search for the presence of Y chromosome material in some cases of Turner syndrome. If this is present there is a high risk of developing gonadoblastoma and dysgerminoma, thus requiring preventive removal of the dysgenetic gonads. In some cases identification of specific X and Y sequences is important for establishing phenotype-karyotype correlations and for adequate genetic counseling. PCR may be needed in some instances to identify the presence or absence of specific Y sequences [16].

There are some karyotype-phenotype correlations, such as: cases with 45, X are more likely to have congenital lymphedema and webbing neck. Cases with a mosaic condition may have secondary amenorheea compared to those with homogeneous X monosomy [10].

In Turner syndrome there is a haploinsufficiency for the SHOX gene, placed on the pseudoautosomal region of both X and Y (Xp22 and Yp11.3), therefore, affected individuals have short stature and skeletal manifestations. The long arm of the X chromosome has genes for both ovarian development and maintenance. Turner females have oocytes during fetal life but they degenerate. It is believed that two functional X chromosomes are needed for normal ovarian development during fetal life.

Genetic counseling provides information about recurrence risk or availability of prenatal diagnosis. Primary amenorrheea, secondary amenorrheea, early onset of menopause can indicate a chromosomal abnormality, most frequently loss of one of the two X chromosomes. Chromosome analysis would detect the changes. During the last years, fluorescence in situ hybridisation (FISH) has allowed to extent the detectability of chromosome aberrations to the submicroscopic level, especially for deletions [6].

Management of the disorder must also take into consideration psychosocial counseling especially regarding short stature which becomes a major concern when entering school and pubertal failure and sterility [8]. Growth retardation, characteristic for Turner syndrome, is frequently severe in cases with thalassemia. This retardation is caused, in part, by the diversion of caloric resources for erythropoesis, as well as by the chronic anemia. Estrogen replacement therapy is needed not only to induce near normal pubertal development, but also to prevent osteoporosis and to reduce the risk of developing cardiovascular disease [2]. It is important to understand that the less severe phenotypes seen today do not exclude the diagnosis, normal looking short girls should be closely monitored. New approaches to cardiac evaluation were suggested to strengthen the ability to detect and prevent potentially life-threatening cardiac complications [11].

Defects in hemoglobin (Hb) involve qualitative as well as quantitative alterations in globin physiology. Beta thalassemia is due to impaired production of beta globin chains, which leads to an excess of alpha globin chains. These chains are unstable, incapable of forming soluble tetramers on their own, and precipitate within

the cell, thus leading to a variety of clinical manifestations. The degree of alpha globin chain excess determines the severity of clinical manifestations, which are profound in homozygous patients and less severe in heterozygotes, who generally have minimal or mild anemia and no symptoms [17]. These individuals are asymptomatic, their condition often coming to light as an incidental finding [7]. Risk factors for thalassemia include: Asian, Chinese, Mediterranean, or African American ethnicity, but also a positive family history of the disorder. Genetic counseling and prenatal screening may be available to those with a family history of this condition who are planning to have children.

Sex chromosome anomalies and some single-gene disorders may show phenotypic overlappings. Cytogenetic investigation is absolutely necessary for the evaluation of all patients with abnormal sexual development or hypogonadism. Physicians should be able to recognize the presenting signs and symptoms of rare disorders and once the diagnosis is confirmed by a chromosome or molecular analysis, they should be able to serve as a valuable source of support for the index case and family [15].

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