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TURNER SYNDROME WITH MOSAICISM 45, X/47, XXX/46,XX AND OCCURRENCE OF PUBERTY

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ABSTRACT

Turner syndrome is characterized by a chromosomal abnormality, due to loss or alteration in one of the x chromosomes. An 11-year-old female patient, from marília, brazil, with a healthy mother and father. Birth without intercurrences, with 38 weeks, cesarean section and weight of 3kg, presenting difficulty for suction in the first months. In childhood, the patient had upper airway infections and recurrent otitis, in addition to recurrent urinary tract infections, which led to an ultrasound of the urinary tract, reporting anatomy without alterations. The karyotype of this children was 45, x(54)/46,xx(1)/47,xxx(45). At the age of 6, treatment with growth hormone was started due to a drop in growth rate, with a good response.

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INTRODUCTION

Turner syndrome is characterized by a chromosomal abnormality due to loss or alteration in one of the X chromosomes, usually associated with genotype 45,X (50% of cases). Occurs in approximately 1:2500 to 1:5000 female newborns. Affected individuals generally present, among other symptoms, short stature, developmental delay, cardiac and renal malformations, gonadal dysgenesis, affecting ovarian functioning, infertility and, to a lesser extent, intellectual deficit and behavioral disorders. Some of the conditions to which they are most susceptible, are responsible for a greater morbidity and mortality of these individuals(Stochholm*et et al., 2006*),however, in approximately 30% of cases, there is the presence of mosaicism (45,X / 46,XX, 45,X / 47,XXX, 45,X / 46,XX / 47,XXX) that may be associated with a better ovarian function than those with different karyotypes (Maciejewska-Jeske *et al.,* 2015). The mosaicism, in general, generates several different clinical presentations among the affected patients, what makes difficult the determination of the diagnosis and the conduct to be taken.

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In this case we will report a case of mosaicism with spontaneous puberty, which is an unusual phenomenon in young people with Turner Syndrome.

Case Presentation

An 11-year-old female patient, born in Marilia with a healthy mother and father. Birth without complications, with 38 weeks, cesarean section and weight of 3KG, presenting difficulty for suction in the first months. In childhood she presented infections of the upper airways and otitis of repetition, in addition to urinary infections that led to the accomplishment of an Ultrasound of urinary tract reporting normal anatomy. She walked with 1 year and 4 months and although she started speech with 1 year it evolved with alterations requiring speech-language therapy, with normal audiometry. At age 3, there was growth within the target height (25th percentile), without phenotypic changes but with language delay, resulting in the search for a Neurologist, at which time the karyotype and the later chromosomal finding were performed, identifying 45, X (54) / 46, XX (1) / 47, XXX (45). The presence of a marked chromosome and absence of an X chromosome (46, X, + sea) were evidenced. In the investigation was performed Echocardiogram that

presented bicuspid aortic valve and Electroencephalogram with frontal lobe immaturity. At the age of 6, treatment with growth hormone was started due to a drop-in growth rate, with a good response. At physical examination, in the Tanner scale, breasts and pubic hair were at stage 1. With 10 years of age, the patient had a spontaneous onset of puberty (breasts and pubic hair in stage 2, Pelvic Ultrasonography with uterus 4cm³, right ovary 1.7cm³, left ovary 1,2cm³, follicle 6mm and exams showed E2 10pg / mL LH: 0.74Mui / ml and bone age 12 years). With 10 years and 7 months uterus of 7.7 cm LH 5.73 mui/ml, FSH 6.9 MUI/ML, estradiol 25 PG/ML. At age 11, the patient presented spontaneous menarche with regular monthly cycles. At the time of menarche, she presented 22cm³ uterus, right ovary 3cm³, left ovary 1.6cm³, E2 45µg/mL, LH 5.13mUI / mL, FSH 5.04mUI / mL, PRL 5.7ng / mL, weight 46KG and height 145.5 cm². The Ethics Committee from Medical School of Marília – UNIMAR under approval protocol number 09132518.4.0000.5496, approved this case report.

DISCUSSION

Turner syndrome presents in 50% of the cases as the absence of the X chromosome, and structural alterations and mosaicismare observed in the remaining groups (Bouchlariotou*et al*., 2010). The mosaicism 45,X / 47,XXX can be caused by postzygotic non-disjunction in cells of normal disomic lineage, resulting in cases of monosomy and trisomy. It is a rare event (approximately 1% of cases of Turner's syndrome), which determines a less severe presentation of the disease compared to 45,Xgenotypes (Maciejewska-Jeske*et al.,* 2015) . Due to the inactivation process of X, the presence of the third X of cells 47, XXX does not by itself lead to the occurrence of relevant symptoms, remaining undiagnosed in many cases. Despite this inactivation, the presence of trisomy causes effects on the development of the syndrome. Malfunction of the gonads can be described, in part, as a result of follicular loss during the first moments of life. However, triple X individuals have greater preservation of ovarian tissue, so that there is a greater probability of residual ovarian functioning. There are several degrees of tissue conservation, varying according to the ratio between 45,X cells and 47,XXX cells during the differentiation between somatic and germ cells, so the degree of gonadal dysgenesis depends on the size of regions of impaired homologous chromosomes. Severe failure of pairing induces the degeneration of all oocytes prior to puberty, whereas a less significant amount contributes to the survival of a considerably larger number of oocytes up to that stage (Bouchlariotou*et al*., 2010; Seifer*et al.,* 1999). Thus, while some present functional absence, others have normal activity and in addition, the existence of gonadal activity can be uni or bilateral (Williams *et al*., 1992).

Therefore, this residual functionality of the ovaries allows the spontaneous occurrence of menarche and a higher level of fertility, which is still inferior. It was verified that the majority of spontaneous pregnancies in women with this syndrome were in cases of mosaicism. There is also a greater likelihood of normal serum levels of sexual steroids and gonadotrophins, thus, secondary sexual characteristics may evolve normally (Doğer*et al., 2015*). Due to the presence of mosaicism 47,XXX the phenotype is attenuated for the changes that are normally found in the karyotype 45,X. However, along with this change one must consider the different amount of cell line distributed in the body (Sybert, 2002). The short stature affects about 95% of the individuals, and the use of Growth Hormone is of utmost importance in the child with Turner's syndrome, which can promote a gain in final height in some cases up to 20 cm. Studies show that the previous introduction at 4 years gives a better result in the final growth. (Linglart *et al.,* 2011) In this way, the treatment should be individualized, verifying the growth rate and IGF-1 for the correct maintenance of the dose. Cardiac malformations, such as bicuspid aortic valve, which is represented by our patient, are found in 20% of the individuals affected by the syndrome, and less than 4% of individuals with 45X / 47XXX karyotype will have renal or cardiovascular changes. (Bouchlariotou *et al*., 2010; Sybert, 2002) It is important to emphasize that the use of GH leads to an increase in stature but does not promote a disproportion in cardiac growth. The use of GH, when performed in the same concentration used in the syndrome cases but in individuals without the deficiency of this hormone and who do not have the disease, can generate an increase in cardiac output and left ventricular mass rapidly. However, studies have shown that treatment with Growth Hormone in children with Turner Syndrome has presented few of these effects, so it is not possible to say that there is a greater susceptibility of these individuals to cardiovascular alterations (Matura *et al*., 2007).

Another hormone commonly used in Turner Syndrome is estrogen, a major initiator of the process of sexual maturity. Therefore, for children with this syndrome to maintain a normal development of puberty, estrogen replacement therapy is indicated. However, this therapy is not used in patients with spontaneous puberty. When applied, it is started from 5 to 10 years, and there is discussion among the authors of the best age to start in order to reach puberty at the correct age, that is between 12 and 14 years of age. Progesterone should be added to therapy after two years of estrogen use or after menarche to reduce the risk of breast or endometrial cancer secondary to prolonged estrogen use (Yang, 2009). Therefore, it is possible to say that combination therapy is the best therapy and the use of estrogens can be oral or in adhesives. The X chromosome influences the development of several brain areas in an intense way. The neuronal functions of the parietal, prefrontal cortex, and tonsil-hippocampal regions are the most affected by it. Thus, the changes present in Turner Syndrome may impair this process, causing cognitive dysfunction in the individual, a characteristic presented in our patient demonstrated by attention deficit and speech delay (Jhang *et al., 2014*). In individuals with mosaicism the diagnosis of Turner syndrome is usually delayed due to low phenotypic expressions. The investigation for pathology may begin in the prenatal period with the appearance of abnormalities in the ultrasound such as increased nuchal translucency, fetal edema, hygroma cystic and anatomical changes in heart and kidney. After birth, identification is established by characteristics such as short stature, delayed growth rate, identification of high levels of FSH in adolescence, lack of development of secondary sexual characteristics and primary amenorrhea (Gonzalez *et al*., 2012).

Conclusion

Correct diagnosis of the karyotype is extremely helpful and should always be performed in girls with short stature, even with few stigmas, where the clinical findings are justified by the presence of certain mosaicisms. The diagnosis of Turner syndrome may be delayed, since the symptoms may be

attenuated by the existence of cells with trisomy X and the medical professional may not think of such a diagnosis, besides such girls may have spontaneous menarche and consequently fertility, the which would further complicate the clinical reasoning for such diagnosis. In this way, is important to emphasize that every girl with short stature should have a karyotype examination. A multidisciplinary follow-up is extremely important to correctly address changes in neuropsychomotor development, growth, and certain congenital abnormalities that are expressed by the patient.

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