Review Article

Indian Journal of Genetics and Molecular Research
Volume 9 Number 2, July-December 2020
DOI: http://dx.doi.org/10.21088/ijgmr.2319.4782.9220.6

Triple X Syndrome: An Appraisal Under Review Study

Dhanesh Kumar Sharma

How to cite this article:
Dhanesh Kumar Sharma / Triple X Syndrome: An Appraisal Under Review Study. Indian J Genet Mol Res. 2020;9(2):57–61

Abstract

The Triple X syndrome is an anomalous genetic condition distinguished by an extra X chromosome in each cell of the female body. This manuscript is prepared with the objectives of giving a better understanding and summarizing the current status of the Triple X syndrome cases and to be used by individuals to understand best about this abnormality. This syndrome was first identified in 1959. The Triple X females are usually with normal fertility and sexual development, so able to conceive children and lead productive lives. Mostly there are no any obvious physical differences other than often taller stature than average in these cases. In some cases the symptoms may be more apparent including developmental, psychological and behavioral problems and may lead to a number of other ill health including work, school, social and relationship problems like learning difficulties and delayed development of speech and language skills; decreased muscle tone / weakness / hypotonia and delayed development of motor skills such as sitting and walking; behavioral and emotional difficulties; seizures and kidney problems. For these problems they need additional support and assistance. The cause of this syndrome is an accidental event during cell division and resulted either during the division of the mother's reproductive cells or during the division of cells at the beginning of development of zygote. The Triple X syndrome is not typically inherited or run from one generation to the next. A form where only a percentage of the body cells contain XXX can also occur. Diagnosis is by the karyotyping or chromosomal analysis. The treatment may include the speech and physical therapy and the counseling. The prevalence rate of the Triple X syndrome is around 1 in 1,000 girls. It is estimated that 90% of those affected are not diagnosed as they either have no or only few symptoms. The parents should talk with a doctor about disquiets with the development of their daughters which will help girls receive an early diagnosis and interventions. The researches have shown that early treatments at younger age are more effective towards normalcy of life in the Triple X cases. Adolescents and adult women presenting with late menarche, menstrual irregularities, or fertility problems should be evaluated first for the premature ovarian failure and Triple X syndrome.

Keywords: Chromosome; Trisomy; Karyotype; Inherit; Superfemale.

Introduction

Overview

The Triple X syndrome or Trisomy X or 47XXX is an anomalous genetic condition distinguished by an extra X chromosome in each cell of the body of a female. In these cases usually females are with normal fertility and sexual development so able to conceive children and lead productive lives. There are no any obvious physical differences other than often taller stature than average and usually with very long legs. They don't understand symptoms

Author's Affiliation: Additional Professor and Head, Department of Anatomy, All India Institute of Medical Sciences, Raipur, Chhattisgarh 492099, India.

Corresponding Author: Dhanesh Kumar Sharma, Additional Professor and Head, Department of Anatomy, All India Institute of Medical Sciences, Raipur, Chhattisgarh 492099, India.

E-mail: dhyanesh.sharma@gmail.com

or experience only mild ignorable symptoms. In some cases the symptoms may be more apparent including developmental, psychological and behavioral problems and may lead to a number of other ill health including work, school, social and relationship problems like learning difficulties and delayed development of speech and language skills; decreased muscle tone / weakness / hypotonia and delayed development of motor skills such as sitting and walking; behavioral and emotional difficulties; seizures and kidney problems.[1] For these problems they need additional support and assistance. The seizures or kidney abnormalities occur in a small number about 10 percent of the affected females. Treatment depends on symptoms and their severity if present and may include the speech and physical therapy and the counseling.

The Triple X syndrome is not inherited or present since birth and resulted as an event or incidence during the process of gametogenesis means the formation of reproductive cells ovum and sperm. An error in the cell division called non-disjunction results in reproductive cells with additional chromosomes and an oocyte or sperm cell may gain an extra copy of the X chromosome as a result of this non-disjunction. The genetic makeup of a child is then contributed with an extra X chromosome and this child will have an extra X chromosome in each of her cells. In some cases, the trisomy X is resulted in the cell divisions in the early stage of the embryonic development. Sometimes the Triple X syndrome may be presented with an extra X chromosome in only some of their cells not all the cells in the body, due to the incorrect cell division in the embryo and termed 46,XX/47,XXX mosaics, usually associated with a fewer symptoms.

Cause

We all know that normally the human body has 46 chromosomes arranged in 23 pairs in each cell including two sex chromosomes. The genes present in the chromosomes carry instructions about various characteristics like height eye color etc. The pair of sex chromosomes presents either XX or XY combination and determines the sex of the person. A mother can give the child only an X chromosome in the female gamete but a father can pass on an X or a Y chromosome in the male gamete. If the zygote receives an X chromosome from the father, then due to the resulted XX pair of sex chromosomes the child becomes genetically a female, but if the zygote receives a Y chromosome from the father, then due to the resulted XY pair of sex chromosomes the child becomes genetically a male. The Triple X cases is due to an accidental event or error before conception or early in the embryonic development, resulting in an additional third X chromosome in the cells either during the division of the mother's reproductive cells or during division of cells during near the beginning of development after fertilization[2] and due to extra X chromosome the karyotype results in 47,XXX in each cell instead of normal karyotype 46,XX.

This accidental or random error causing the Triple X situation may be resulted mostly by the non-disjunction of either the ovum or the sperm cell which divides incorrectly, resulting in an extra X chromosome in the zygote and so all the cells in the growing body will have an extra X chromosome. Occasionally, the child has a mosaic form of the Triple X syndrome where only some cells in the body have the extra X chromosome and only a percentage of the body cells contain XXX by the incorrect cell division and a random error early in the embryonic development. Females with the mosaic form may have less obvious symptoms. The Triple X syndrome is a genetic disorder due to a random genetic error but it is usually not inherited or run from one generation to the next.[1]

Symptoms and signs

Usually it is very difficult to generalize or simplify the effects of this syndrome and so the vast majority of triple X females remain never diagnosed as they are healthy and have no any obvious symptom. Signs and symptoms vary greatly amongst female with triple X syndrome. Many experience either no noticeable effects or only mild symptoms. Mostly Triple X syndrome is detected often when parents talked with a doctor about disquiets with the development of their daughter's development. Certainly this helps girls receive an early diagnosis and early interventions; and researches have shown that early treatments at younger age are more effective. Being taller than standard normal height is usually the most typical physical feature. Most females with triple X syndrome have normal sexual development and fertility having normal ability for pregnancy. Mostly their intelligence level is in the normal range and possibly a little lower level than their siblings and only few cases may be associated with the intellectual disabilities and behavioral troubles.

As only one X chromosome is active at any time whereas lionization and inactivation of other two inactive X chromosomes in all female cells in triple X syndrome present two Barr bodies in each cell. There are seldom any observable physical

anomalies in triple X females, other than being taller than average. Apart from the tall stature, the signs and symptoms in females with triple X syndrome sometimes may include an increased risk of the vertical skin folds covering the inner corners of the eyes i.e. epicanthal folds, widely spaced eyes called hypertelorism, decreased muscle tone and curved little finger towards the 4th finger called clinodactyly;[2] a small head or microcephaly, scoliosis and poor coordination etc. The diagnosis of the Triple X cases is by the karyotyping or chromosomal analysis[3] and rarely the Tetrasomy X and Pentasomy X syndromes may also be detected with most of the characteristics of the Trisomy X and more significant developmental delays and dysmorphic features than the Trisomy X. The congenital malformations and their severity are more in the Pentasomy X and it shows a typical short stature, which is absent in the Triple X syndrome.[4] The electroencephalography may present abnormalities.[5]

Some females with the Triple X syndrome may be associated with the developmental, psychological and behavioral problems and may lead to a number of other ill health including work, school, social and relationship problems and need for additional support or assistance. There may be delayed development of social, speech, language, learning skills such as reading, understanding or math as well as fine and gross motor skills like sitting and walking; on average 20 points decreased IQs and problems with reading and understanding math; poor coordination, self-esteem and self confidence; attention deficit hyperactivity disorder (ADHD), deficit in memory, judgment and information processing; anxiety and depression.[2] These problems may ease as they get older and reach adulthood. A steady home environment and setting can improve some of the symptoms in the triple X syndrome cases.[5]

Less often, the Triple X syndrome may develop abnormal ovaries and/or uterus, a delayed or an early onset of puberty and problems with fertility; premature ovarian failure or ovary abnormalities, kidney and heart problems; frequent urinary tract infections (UTIs), stomach pain, constipation, flat feet; and abnormal shape of sternum, chest wall and ribcage called pectus excavatum.[6] Adolescents and adult women presenting with late menarche, menstrual irregularities, or fertility problems should be evaluated for premature ovarian failure and then triple X syndrome. Presence of seizure disorders and EEG abnormalities vary between 0 to 65% by various group studies and means of ascertainment but in the largest cohorts clinical seizures are present in approximately 15% of cases. The absence, partial and generalized seizures have been claimed with good comeback by the anticonvulsant therapies.[7,8] The finding of white matter high intensity foci in 27% of females with trisomy X has been reported, which is similar to those seen in other sex chromosome aneuploidy groups and populations like 48,XXYY and 49,XXXXY.[9]

Diagnosis

Usually the Triple X cases are never diagnosed and may remain undiagnosed in their lives because these females are mostly healthy and show no remarkable symptoms and noticeable signs of this syndrome. They come in view and the diagnosis may be discovered while checking other issues or being tested for other medical reasons usually in the later period in life. The Triple X cases may also be discovered during prenatal testing of the child for some other genetic disorders. If a Triple X case is suspected on the basis of signs and symptoms, then it can be confirmed by a genetic testing called karyotyping i.e. chromosome analysis using a blood sample. The genetic counseling can help to gain comprehensive information about Triple X syndrome in addition to the genetic testing. In prenatal status the amniocentesis or chorionic villus sampling can be applied for diagnosing the Triple X cases. One study has claimed that 76% of the prenatally diagnosed fetuses with Triple-X were aborted in Denmark between year 1970 and 1984. This figure dropped to 56% with the improved information by 1987 and the number of abortions diminished. Another study reported that in Netherlands between year 1991 and 2000, 33% cases were elected to be aborted when confronted with a prenatal diagnosis of Triple X. With the balanced information to the forthcoming parents about the prenatal diagnosis of Triple X cases, the incidence of voluntary termination of pregnancy or abortion can be reduced.[10]

Treatment

The Triple X syndrome itself has no cure as the chromosome error causing triple X syndrome is non repairable, so the treatment is based on the symptoms and the needs and may include speech therapy, physical therapy and counseling. The prevalence rate of the Triple X cases is around 1 in 1,000 females. It is estimated that 90% of those affected are not diagnosed as they either having no

any notable difficulty or only with few symptoms. It was first identified in 1959[11] when a woman with a 47,XXX karyotype was reported by Patricia A. Jacobs group at Western General Hospital in Edinburgh, Scotland, That woman was with 35 years in age, 5 ft. 9 in. / 176 cm in height and 128 lb. / 58.2 kg weight. She had premature ovarian failure at age 19; and her mother 41 and father 40 years at the time of her conception. Jacobs group called this triple X woman a "superfemale" but this term which was without more ado criticized and could not be accepted as based on the incorrect assumption and hypothesis that the sex-determination system in mammals was similar as in the fruit fly Drosophila.[12] Later in 1960, Bernard Lennox a British pathologist, geneticist and the principal consultant on medical terms for the Oxford English Dictionary, recommended the term XXX syndrome.

There is no permanent cure for the Triple X syndrome but the treatment can help in alleviation with the specific symptoms. Depending on the age of a female with the Triple X, her noticeable symptoms and their severity, the options regarding the treatment vary. As already mentioned, finding the services early is more important towards increasing the ability to help a Triple X female live a healthier and more productive life by minimizing their symptoms.[6] Treatments should include the regular doctor visits to scrutinize the girl's development, any delay in societal adjustment or deficiencies, language disabilities or health problems. After confirmation and diagnosis a prompt treatment can be scheduled for any associated developmental delays, learning disabilities or health problems. The doctor should recommend periodic screenings throughout childhood and even in adulthood in suspicious cases. Then only early intervention services like speech, occupational, physical or developmental therapy can be applied as soon as requirements are recognised.

Cope and support

The females with Triple X syndrome can lead a complete and happy life however; sometimes the help and support are needed in the form of some strategies. The support groups help and support by offering information and advice on coping, ways to assemble and chat with others in similar circumstances. The coping learning disability by the disability support resource is a little challenging job. The trusted friend or family member can adopt ways to relieve her stress overwhelming situation. The parent's responsibilities are important because they have to be careful about unusual symptoms and developmental milestones in their child like learning to say first words or learning to walk etc. and any problem with learning, emotions or behavior. They are expected to key their personal information regarding pregnancy, any significant illnesses or any medications used.

The educational support services play an important part towards managing this syndrome. The educational assistance, techniques and strategies will help in learning disability to be successful in school and daily routine life. The educational support can educate girls about the ways to keep swiftness in school. Some girls may be eligible for some education plan and an individualized educational program (IEP), which are planned to help children with specialized needs in genetic disorders. Parallely the early intervention services can be very supportive and more effective in managing the Triple X cases to provide speech / language, occupational, physical or developmental therapies in the initial period of their life or as early as the concerns are recognized to help increase strength, coordination, confidence and interact better with other children. As the females with Triple X syndrome are sensitive to develop anxiety, behavioral and emotional problems, the supportive environment as well as psychological counseling will definitely help teach the female and her family how to express love, encouragement and moral support and how to discourage behaviors cause negatively impact in learning and social functioning. The Counseling of the whole family is necessarily required to better understand about the Triple X syndrome and help the girl to live a productive life. The assistance and support in daily functioning like routine living, social opportunities and employment play an important role in the treatment of these cases.

The early interventions of treatment in this syndrome should be considered at her infancy period for the physical therapy, age of 15 month for the speech delay, 6-7 years for the reading and the learning issues; and 8-9 years for the anxiety or the depression.[10] It is very important for the parents to consult the physician if they find some concerns regarding the physical and the emotional development in their daughters. The Triple X syndrome at their young age may develop speech, learning or social adjustment difficulties and find themselves with low self-esteem and then lead to school or social problems like trouble in making friends and struggles at school. The proper counseling and sincere treatment can guide these girls the practical skills to help making friends

and feel more confident in school; and educational services can help them succeed academically.

Conclusion

The Triple X syndrome was first identified in 1959 as a genetic condition distinguished by an extra X chromosome in each cell of the body of a female. In these cases, there are no any obvious physical differences other than often taller stature of these females with the normal fertility and sexual life. Sometimes it may be associated with the developmental, psychological and behavioral problems; and may lead to a number of other ill health including work, school, social and relationship problems; and then there is a need for the additional support or assistance. This syndrome is due to an accidental event resulted either during the division of the mother's reproductive cells or during division of cells during the initial stage or beginning of the development of embryo. It is not typically inherited or run from one generation to the next. The diagnosis is by the karyotyping and the treatment helps in alleviation with specific symptoms; and may include the speech therapy, physical therapy and counseling. The parents should talk with a doctor about disquiets with the development of their daughters to detect this syndrome and certainly this helps girls receive an early diagnosis and early interventions, as researches have shown that the early treatments at younger age are more effective towards normalcy of life in this syndrome.

Reference:

1. GHR (Genetics Home reference). Triple X Syndrome. 26 September 2016.
2. Tartaglia NR, Howell S, Sutherland A, Wilson R, Wilson L. A review of trisomy X (47, XXX). Orphanet Journal of Rare Diseases. 11 May 2010;5:8.
3. GARD (Genetic and Rare Diseases). 47 XXX syndrome. 26 September 2016.
4. Ottesen A, Aksglaede L, Garn I, Tartaglia N, Tassone F, Gravholt C, Bojesen A, Sorensen K, Jorgensen N, Rajpert-De Meyts E, Gerdes T, Lind AM, Kjaergaard S, Juul A. Increased number of sex chromosomes affects height in a non-linear fashion. Am J Med Genet A. 2010;152(5):1206-12.
5. Otter M, Schrander-Stumpel CT, Curfs LM. Triple X syndrome: a review of the literature. European Journal of Human Genetics. March 2010;18(3):265-71.
6. Judith L Ross. Triple X Syndrome. KidsHealth / for Parents. Reviewed: August 2017.
7. Grosso S, Farnetani MA, Di Bartolo RM, Berardi R, Pucci L, Mostardini R, Anichini C, Bartalini G, Galimberti D, Morgese G, Balestri P. Electroencephalographic and epileptic patterns in X chromosome anomalies. J Clin Neurophysiol. 2004;21(4):249-53.
8. Roubertie A, Humbertclaude V, Leydet J, Lefort G, Echenne B. Partial epilepsy and 47,XXX karyotype: report of four cases. Pediatr Neurol. 2006;35(1):69-74.
9. Hoffman TL, Vossough A, Ficicioglu C, Visootsak J. Brain magnetic resonance imaging findings in 49,XXXXY syndrome. Pediatr Neurol. 2008;38(6):450-3.
10. Schrander-Stumpel C (2005). Triple-X-Syndrome or Trisomy X (PDF). Patient Care. 2005;32(6):15-21. Archived from the original on 2011-07-24. Retrieved 2010-07-28.
11. Wright David Downs. The history of a disability. OUP Oxford. 2011;159.
12. Ferguson-Smith Malcolm A. Putting medical genetics into practice. Annual Review of Genomics and Human Genetics. September 2011;12:1-23.