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Turner Syndrome: An Update Review

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Abstract:- Turner syndrome was first described by Oklahoman physician Henri Turner in 1938. This syndrome can occur in females who have an absent X chromosome, either completely or partially. The two primary forms of TS are mosaic and classical. Data from newborn genetic screening and epidemiology in the US, Europe, and Japan suggest that it affects 1% to 3% of live female infants. Webbed neck, swollen hands and feet, shield-shaped chest, low hairline, droopy eyelids, high-arched palate, and elevated elbow carrying angle are among the physical traits associated with TS. Standard karyotyping, which looks at the chromosomes of 30 peripheral cells, can confirm the presence of Turner syndrome. Cardiovascular irregularity, hypogonadotropic hypogonadism, infertility, skeletal abnormalities, and autoimmune illnesses are among the complications associated with TS. The main treatment for TS is growth hormone therapy, with different approaches based on the organ involved.

Keywords:- *Turner Syndrome, Chromosome, Short Stature Homeobox, Hormone Replacement Therapy, Karyotype.*

I. INTRODUCTIONS

Turner syndrome was first described by Oklahoman physician Henri Turner in 1938. Another name for the syndrome is congenital ovarian hypoplasia. This is, by far, the most common abnormality of the female chromosome. This disease is brought on by the complete or partial absence of an X chromosome [1]. The missing genes result in the abnormalities and traits seen in women with Turner's syndrome. Turner's syndrome is also known as monosomy X, 45X, and Ullrich-Turner syndrome. The effects and severity of the sickness vary widely depending on the degree of chromosomal abnormality. Turner's syndrome affects about 1% of all newborn girls. However, because of its prenatal prevalence, this defect might be more common than first thought. With this chromosomal abnormality, only about 1% of fetuses reach term and 10% of losses are linked to it. [2] Classical and mosaic TS are the two primary varieties. Two cell lines coexist in mosaic Turner, whereas one X chromosome is entirely missing in classical TS. A TS clinical diagnosis can be confirmed by a karyotype. The short stature homeobox (SHOX) gene, which is situated on the distal end of the short arm of chromosome 10, is haploinsufficient in people who are short in stature. Keep in mind that the growth hormone (GH)/insulin-like growth factor axis is normal in these girls. Physically, tiny stature, webbed neck, cardiac issues, decreased glucose tolerance, thyroid disease, hearing loss, and ovarian failure are all indicative of TS. Although there is a lot of variance among these phenotypes, short height, and gonadal dysgenesis are the most prevalent phenotypic characteristics. The two major treatments for TS in females are growth hormone (GH) and hormone replacement therapy (HRT). [2,3]

II. INCIDENCE AND PREVALENCE

Before karyotyping was available, Oklahoman physician Henri Turner (1938) characterized seven women with cubitus valgus, diminutive height, sexual immaturity, and neck webbing as a clinical disorder. However, Otto Ulrich had previously described a girl with the same phenotypic characteristics who was the same age. Turner syndrome is linked to most sex chromosomal abnormalities in females. Data from newborn genetic screening and epidemiology in the US, Europe, and Japan suggest that it affects 1% to 3% of live female infants. Since some people with Turner syndrome may not receive treatment because of a milder phenotype, it is difficult to pinpoint the true incidence of the condition. [4] A patient may not receive a diagnosis until later in life if their phenotype is modest. All racial and ethnic groups, as well as all countries, have a comparatively consistent frequency of Turner syndrome. However, it appears that some countries are witnessing a decline in the predominance at birth. Prenatal ultrasound screening has increased as a result of pregnant women choosing to terminate their pregnancies when they learn their fetuses have Turner syndrome. On the other hand, X chromosomal monosomy (45, X) is linked to a very high stillbirth rate. At least 10 percent of spontaneous abortions are genotyped 45, X. [3,4]

III. CLINICAL FEATURES OF TURNER'S SYNDROME

Apart from partial deletions of the long (Xq) or short (Xp) arms, entire monosomy X is also associated with TS traits. Specific traits within the clinical spectrum of TS could be connected to specific X chromosomal deletions. Of them, ovarian failure, or gonadal dysgenesis, is one of the most common features. Low levels of circulating estrogen, insufficient pubertal development, and infertility are the results. Additional physical characteristics of TS include short stature and any of several specific somatic abnormalities, including webbed neck, swollen hands and feet, low hairline, shield-shaped chest, droopy eyelids,

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hearing loss, high-arched palate, increased elbow carrying angle (cubitus valgus), short fourth or fifth metacarpals, renal malformations, multiple pigmented nevi, lymphedema, impaired glucose tolerance, autoimmune thyroid disease, and hypertension. Short stature is frequently visible in early life. Adult height measurements for TS women who had not undergone growth hormone treatment ranged from 146 to 148.5 cm. Better growth is encouraged by growth hormone therapy. Certain physical traits, including cubitus valgus, short metacarpals, and edema, appear in childhood and persist throughout age, whereas other physical traits, such as nevi, appear in adolescence and adulthood. [5,6] Two examples of complex multifactorial traits that usually appear in youth or are identified in adulthood are impaired glucose tolerance and hypertension. Treating this patient population requires a multidisciplinary team of healthcare specialists because of the various systems involved in TS. Turner Syndrome Consensus Study Group has published a clinical practice guideline for the management of females with Turner's syndrome. This suggestion focuses on comprehensive care, which includes prenatal and postnatal diagnosis and monitoring for linked problems in the areas of cardiovascular, vision, hearing, dental, renal, skeletal, endocrine, immune system, and psychosocial adjustment. Growth hormone administration to maximize height and estrogen therapy to induce puberty are well-designed, tried-and-true protocols. [7]

IV. PATHOPHYSIOLOGY OF TS

A. Karytypes

A lack of X chromosomal material is a common feature of women with a range of karyotypes, including those who may develop the clinical illness known as Turner syndrome. Karyotypes can include 45, X (complete loss of one X chromosome), ring chromosomes, Y-chromosomal material, isochromosomes of the p or q arm, and many more. Examples of mosaics of these chromosomes are 45, X/46, XX; 45, X/47, XXX. Twenty percent of women with Turner syndrome have an isochromosome, forty to fifty percent have the 45, X karyotype, fifteen to twenty-five per cent have 45, X/46, XX mosaicism, and a tiny percentage have ring X chromosomes. In addition, around 3% of women with 45, X/46, or XY chromosomal material are among the 10-12% of women that have this characteristic. [8]

B. Associated Genes

Short stature homeobox protein (SHOX), an X and Y chromosomal pseudoautosomal region gene, is the only one linked to the Turner syndrome phenotype thus far. Turner syndrome growth loss could be explained by the fact that SHOX can evade X-inactivation and that its reduced expression exacerbates the disease. Scoliosis, micrognathia, a high-arched mouth, Madelung deformity, and small legs (but normal sitting height) are other common characteristics of SHOX haploinsufficiency. The SHOX gene product interacts with genes encoding SOX5, SOX6, and SOX9, members of the SRY-related high mobility group box family of transcription factors involved in cell fate determination, in addition to regulating the expression of fibroblast growth factor receptor 3 (FGFR3) and natriuretic peptides B (NPPB). [3,7]

C. Epigenetics & RNA Expression

Research on epigenetics and RNA expression in blood from patients with Turner syndrome conducted in 2015 and 2016 implicates additional autosomal genes that were not previously associated with the condition. [2] These results might affect our understanding of the genetic composition of Turner syndrome. The Turner syndrome genome has fewer regions of hypermethylation than the genomes of women with 46, XX, and RNA expression anomalies affecting X chromosomal genes and autosomal genes. Moreover, there is hypomethylation throughout the entire genome. Keep in mind that women with 45, X only have one X chromosome, so any symptom linked to Turner syndrome may be explained by escape genes—X chromosome genes that are known to elude X-inactivation. [8]

V. DIAGNOSIS OF TS

Standard karyotyping, which looks at the chromosomes of 30 peripheral cells, can confirm the presence of Turner syndrome. In half or more of the individuals, there will be either a mixture of normal cells with one extra X chromosome (45, X/46, XX; mosaic Turner syndrome) or normal cells with one additional X chromosome (45, X). A mosaic result may not always appropriately reflect severity since karyotyping concentrates on lymphocytes rather than pertinent organs (such as the brain, heart, or ovaries).[7,9]

By sending the entire amount of blood in a green-top sodium heparin tube, at room temperature, to a lab for analysis, one can acquire a karyotype. The karyotyping process lasts for a week. X-specific fluorescence in situ hybridization can confirm monosomy X in less than a day when a prompt diagnosis is required, such as when parents are concerned or a serious clinical crisis arises.[10]

Turner syndrome can be caused by any of the sex chromosome abnormalities, however, it is most commonly associated with the X chromosome. These include ring X, deletion Xp, and an aberrant Y chromosome. Because they have a 12% risk of developing gonadoblastoma, those with Y chromosomal material should undergo imaging studies in addition to a laparoscopic gonadectomy, which removes testicular tissue.[11]

Turner syndrome is sometimes not recognized until much later in life in girls who are small in stature. According to one study, it takes seven years on average for a woman's short height to show up clinically on her growth curves and for a diagnosis to be made. In one case study, it was found that 4% of females with isolated short stature who were referred for genetic testing had Turner syndrome, independent of their family's history of height. Amenorrhoea or other dubious phenotypic features were used to diagnose Turner syndrome in nearly 30% of the girls who were referred for therapy. If a girl's height is more than two standard deviations below the average for her age, she should be classified as a karyotype. [7,10,11]

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VI. COMPLICATIONS OF TS

A. *Disorders Associated with Turner Syndrome Hypogonadotropic Hypogonadism, Infertility, and Sexual Function*

A small proportion of women can maintain spontaneous fertility; most people with Turner syndrome also have hypogonadotropic hypogonadism, which results in primary or secondary amenorrhoea and ultimately infertility. Turner syndrome46 is characterized by an early and fast loss of oocytes from the ovaries, while the precise origins of this phenotype are still unknown. During the onset of puberty, breast growth happens spontaneously in 21–50% of teenagers with Turner syndrome. [11,12]

B. *Cardiovascular Abnormality*

Epidemiological research revealed that the overall death rate for TS patients was three times greater than that of the general population. Cardiovascular events are a substantial risk factor for 41% of patients. Compared to the general population, TS patients have a higher prevalence of congenital cardiovascular abnormalities. Heart valve failure is a frequent anomaly overall, and aortic bicuspid deformity is particularly common in TS patients. [12] Most TS-related deaths are due to aortic dissection-caused aneurysms; aortic youth have a smaller aortic diameter than the general population; and aortic surgery is required in TS patients older than 18 years with an ascending aortic size index greater than 2.5 cm/m2 to prevent aortic dissection. Due to ethnic heterogeneity and small sample size, more research is needed to precisely identify the incidence of cardiovascular illness in TS patients. [13]

C. *Skeletal Abnormalities*

In terms of TS issues, fractures rank among the most dangerous. There is no proof that TS raises the risk of fracture in children or adolescents, whereas women with TS have a roughly 25% increased risk of fracture, most commonly forearm fractures. Tomographic data from TS patients has been questioned due to studies of elderly people without estrogen or with delayed or insufficient treatment; hence, the stated prevalence of fractures may be inflated. [8,13]

D. *Autoimmune Diseases*

Secondary autoimmune disease is one of the most prominent features of X chromosomal aneuploidy-related TS. The most common autoimmune disease brought on by TS is thyroiditis, although it can also result in colitis, celiac disease, psoriasis, type 1 diabetes, and other autoimmune disorders. 3.2% of TS patients who underwent follow-up studies went on to develop autoimmune thyroiditis. [14] Chinese people with TS have a higher risk of Hashimoto's thyroiditis than the Chinese population as a whole, where the prevalence of the condition ranges from 0.4% to 1.5%. Compared with children in other regions of the world, children with TS are considerably more likely to develop Hashimoto's thyroiditis. TS sufferers are more likely than the general population to have celiac disease; among the patients analyzed, the illness's frequency ranges from 2.2% to 8.1%. The signs of osteoporosis, short stature, and hypogonadism can all be exacerbated by celiac disease. The prevalence of various autoimmune diseases has some effect on TS patients. [15]

VII. TREATMENT

A. *Short Stature*

Girls with Turner syndrome typically have delayed growth and are somewhat short in stature. Turner syndrome is not characterized by a deficiency of growth hormone. Growth hormone treatment, on the other hand, is very beneficial for patients and should start as soon as the patient's height falls below 5% of their chronological age. [16] If the disease is not sufficiently treated, the estimated adult height is 20 centimeters less than the average adult female's height. Patients should continue receiving growth hormone therapy until they reach adult height and are no longer able to grow anymore. Sometimes, once a patient starts taking growth hormone therapy, underlying scoliosis becomes visible. Consequently, it is critical to periodically assess the patients' spines as they receive therapy. When a patient develops scoliosis, they should speak with an orthopedic surgeon about bracing or other corrective surgical alternatives. The administration of growth hormone may also cause intracranial hypertension, slipping capital femoral epiphyses, and pancreatitis. Patients who require additional growth support may benefit from delayed pubertal induction, oxandrolone, or growth hormone. [16,17]

B. *Cardiac*

Turner syndrome is often linked to an irregular heartbeat. A cardiologist should check for a longer QT interval on the electrocardiogram (ECG) when diagnosing a patient. Both the upper and lower limbs should have their blood pressure checked, and any abnormalities in the heart should be found by an echocardiogram or cardiac magnetic resonance imaging (MRI). Steer clear of all psychiatric, macrolide, fluoroquinolone, metronidazole, antifungal, antiretroviral, and antiarrhythmic drugs if you want to keep your QT interval lengthy. If aortic coarctation is found, it must be corrected surgically. [18] Patients should routinely have cardiac MRIs or echocardiograms checked for aortic dilatation throughout their lives. Keep your blood pressure within normal limits to lower your chance of aortic dilatation and dissection. To manage blood pressure, beta-blockers should be used first, and then ACE inhibitors. [15]

C. *Cognitive Function/Learning Disabilities*

Individualized testing and training may be beneficial for many females with Turner syndrome who struggle academically despite having average intelligence.

D. *Hearing Loss*

It is recommended that hearing be assessed regularly throughout life, with children and adults undergoing audiology evaluations every three and five years, respectively. [18]

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E. Renal

Renal ultrasonography is a crucial diagnostic tool. Common renal abnormalities in Turner syndrome include mal-rotated kidneys, positional/horseshoe kidneys, and collection system anomalies. Obstacles brought on by abnormalities in the ureteropelvic junction can cause hydronephrosis and raise the risk of pyelonephritis. If any abnormalities are found, a referral to nephrology should be made. [17]

F. Ovarian Failure

In girls with Turner syndrome, primary amenorrhoea or delayed puberty as a result of early ovarian failure are common symptoms. Testing serum AMH and FSH should be done between the ages of 10 and 11. One potential predictor of ovarian function is spontaneous puberty, which is more common in people with detectable serum AMH levels. If a girl is not growing breasts by the time she is 11 or 12 years old, she needs to start estrogen replacement therapy. [19] Although spontaneous puberty may occur in virtually all girls with Turner syndrome, it usually ends in primary ovarian insufficiency. Nevertheless, for the majority of these girls, estrogen therapy is still necessary. After that, cyclic progestins are added to the dosage to stop endometrial hyperplasia and cause cyclic uterine bleeding. When gonadotropin levels are high or AMH levels are low, estrogen medication should be initiated between the ages of 11 and 12. To mimic the typical puberty process, therapy can start at dosages ranging from a tenth to an eighteenth of the adult replacement dose. Doses can then be raised every six months until the patient reaches the adult dosage. Cryopreservation of ovarian tissue or oocytes is a common treatment for people with Turner syndrome. Children under the age of twelve should not consider this option, and ovarian function needs to be proven before further exploration. [11,20] Insufficient egg production from the ovaries prevents most women with Turner syndrome from becoming pregnant. Using donor oocytes for in vitro fertilization is one way to start a family. [16,20]

G. Osteoporosis/Bone Health

Low bone mineral density and fractures are common in those with Turner syndrome. Estrogen replacement treatment lowers their risk in combination with vitamin D and calcium supplements. Patients with Turner syndrome should be screened for scoliosis once a year and every six months if they are on growth hormone treatment, as the disease increases the risk for deformity. [20]

H. Screening for other Comorbidities

Tissue transglutaminase immunoglobulin A antibody measurements in celiac disease-afflicted children should begin at around age two and be repeated every two years after that. [18] For autoimmune thyroiditis, TSH and free or total T4 measurements should be made annually, beginning at the age of four. Once a child is ten, ALT, AST, GGT, and alkaline phosphatase should be tested annually for liver disease. Even though Turner syndrome frequently results in elevated lab results, if the abnormal levels persist and exceed twice the usual range, a hepatologist should be consulted for further evaluation. To detect hyperglycemia and metabolic syndrome, it is recommended that hemoglobin A1c be assessed annually beginning at the age of 10. To identify dyslipidemia, yearly lipid panel testing should be performed on all individuals with a history of cardiovascular disease or any risk factor for cardiovascular disease. Measure blood 25-hydroxyvitamin D levels every two to three years starting at age nine or eleven and continuing thereafter to prevent vitamin D insufficiency. [20] Y chromosome screening for gonadoblastoma should be performed in patients with Turner syndrome, virilization, or marker chromosomal elements on karyotype. If the Y chromosome is found, it is advised to remove the gonads as this reduces the risk of gonadoblastoma. [21]

I. Children

The treatment of congenital heart disease and cardiovascular surveillance are essential parts of managing Turner syndrome in children. Growth hormone therapy promotes linear growth and can be initiated as early as 12 to 24 months of age. Initiated often in the preteen years, supplemental estrogen therapy preserves bone mineral density and fosters sexual development. With growth hormone and estrogen therapy, the average adult height of patients with Turner syndrome increases to 5 feet, 8 inches (150 cm) from their current 4 feet, 8 inches (140 cm) average. Growth hormone medication is typically discontinued once the patient reaches the bone age of fourteen, in contrast to sex hormone therapy, which is occasionally continued into life. [21] Patients with Turner syndrome require continuous monitoring of thyroid function, liver enzymes, fasting lipids, and glucose levels. They also require audiometry to identify sensorineural or conductive hearing loss resulting from recurrent otitis media. The Barlow/Ortolani maneuvers should be used with caution when evaluating newborns and young children with Turner syndrome for congenital hip dislocation. To screen for hyperopia and strabismus, a pediatric ophthalmologist should be seen if the kid is older than one year. Throughout the diagnostic process, ultrasonography should be performed to identify congenital renal anomalies. Every two to four years, females over four should get a tissue transglutaminase immunoglobulin A test to check for celiac disease. Patients seven years of age and older should have an orthodontic assessment to identify malocclusion and other dental problems. Teenagers should have their kyphosis and scoliosis checked as soon as possible. [21, 22]

J. Adults

A common concern amongst individuals with Turner syndrome is the development of their sexuality and fertility. Usually, during the fetal stage or the early years of life, the ovaries deteriorate while they are still developing. Given that 2 to 5 percent of patients with Turner syndrome experience spontaneous menstruation and births, those who engage in sexual activity should be counseled about birth control. Significant 46, XX/45, X mosaicism, with normal cell populations present in the ovaries, may account for this. Turner syndrome patients frequently see their primary care physicians for guidance with infertility [23]. Age-appropriate counseling for infertility treatments might help alleviate some of the emotional burden associated with the diagnosis. To

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study young women with Turner syndrome, in vitro fertilization techniques are used, which involve oocyte harvesting and freezing before the completion of ovarian regression. It is essential to obtain a heart echocardiogram or magnetic resonance imaging (MRI) before attempting to conceive due to the elevated risks associated with both naturally occurring and assisted pregnancies. Primary care physicians should be in charge of the pregnancy as an essential part of a multidisciplinary team that also includes experts in cardiology, high-risk obstetrics, and reproductive endocrinology. [24] Continuing sex hormone prescription, controlling atherogenic cardiovascular risk factors (e.g., hypertension, diabetes, and hyperlipidemia), and offering reproductive counseling are all part of the treatment for Turner syndrome in adults. To prevent osteoporosis, further precautions include taking calcium and vitamin D supplements. Adults should get a dual-energy x-ray absorption technology bone mineral density scan on their first visit. Every five to ten years, an adult woman should have an MRI or echocardiography of her aorta to determine whether she requires surgery to correct substantial aortic root dilatation, which occurs in 8 to 42% of cases over time. [24]

VIII. CONCLUSION

Turner syndrome is a chromosomal disorder characterized by the partial or complete absence of an X chromosome in females. It presents a wide range of clinical features, including short stature, gonadal dysgenesis, cardiovascular abnormalities, skeletal issues, autoimmune diseases, and infertility. The diagnosis relies on karyotyping, and treatment involves hormone replacement therapy, growth hormone therapy, and addressing associated complications through multidisciplinary care. Early diagnosis and comprehensive management are essential for improving outcomes and quality of life in individuals with Turner syndrome.

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