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Perspective

Multisystem Involvement in Turner Syndrome: Genetic and Clinical Aspects

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DESCRIPTION

Turner Syndrome (TS) is a chromosomal disorder affecting approximately 1 in 2,500 live female births and is characterized by the partial or complete absence of one X chromosome (45,X or mosaic variants). First described in 1938, TS is now recognized as a multisystem disorder with highly variable phenotypic features. From short stature and gonadal dysgenesis to cardiovascular, renal, endocrine, and neurocognitive anomalies, the clinical presentation of TS extends well beyond the reproductive system. Advances in genetics have provided a clearer understanding of how specific gene deletions or haploinsufficiencies contribute to this diverse clinical spectrum.

The underlying genetic abnormality in TS typically involves monosomy X (45,X), but mosaicism (such as 45,X/46,XX or 45,X/46,XY) is also common and can influence the severity of clinical manifestations. The complete loss or partial deletion of X chromosome material leads to haploinsufficiency of several genes that escape X-inactivation and are normally expressed from both X chromosomes. One of the most critical genes implicated in the phenotype of TS is the (Short Stature Homeobox gene (*SHOX* gene), located in the pseudoautosomal region of the X chromosome. Haploinsufficiency of *SHOX* is directly associated with the short stature observed in nearly all individuals with TS, and in some cases, skeletal anomalies such as cubitus valgus and Madelung deformity.

Apart from short stature, gonadal dysgenesis is a hallmark of TS. The ovaries are typically replaced by streak tissue, leading to primary amenorrhea and infertility. These features are largely due to the loss of genes required for ovarian development and maintenance. Estrogen replacement therapy is often required to induce and maintain secondary sexual characteristics and support bone health. Growth Hormone (GH) therapy, when initiated early, has been shown to significantly improve adult height outcomes, especially when combined with low-dose estrogen at the appropriate time.

Cardiovascular anomalies are among the most serious clinical features of TS, contributing to increased morbidity and mortality. Bicuspid aortic valve, coarctation of the aorta, and aortic root dilatation are commonly observed. Regular cardiac evaluations using echocardiography or cardiac MRI are essential, especially given the risk of aortic dissection in adulthood. Electrocardiogram (ECG) monitoring is also important, as some individuals exhibit conduction abnormalities or QT interval prolongation. Renal anomalies, including horseshoe kidney and malrotation, occur in approximately 30%-40% of individuals with TS. While these often do not impair renal function, they may predispose to urinary tract infections or hypertension. Blood pressure monitoring is therefore an integral part of long-term care.

The endocrine system is frequently affected. In addition to gonadal failure, individuals with TS are at increased risk for autoimmune thyroiditis, type 2 diabetes, and osteoporosis. Regular screening for thyroid function and glucose metabolism is recommended. The increased prevalence of metabolic syndrome in TS underscores the importance of lifestyle interventions alongside clinical management. Neurocognitive and psychosocial aspects of TS are often under-recognized but play a key role in quality of life. While general intelligence is usually within the normal range, specific deficits in visual-spatial processing, executive function, and non-verbal memory are common. These challenges can impact academic performance and daily functioning. Early neuropsychological assessment and individualized educational support are key components of comprehensive care.

Hearing loss, both sensorineural and conductive, is another common feature of TS and can affect language development and communication. Regular audiologic evaluations are necessary, especially during childhood and adolescence. Additionally, lymphedema, especially in infancy, and characteristic physical features such as a webbed neck, low posterior hairline, and broad chest may assist in early diagnosis. Genetic counseling is essential for families and individuals affected by TS. It provides education about the condition, recurrence risks, and reproductive options, including the potential for pregnancy through assisted reproductive technologies such as oocyte donation.

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CONCLUSION

Turner syndrome is a complex disorder involving multiple organ systems, with significant variability in presentation. The genetic basis, particularly involving haploinsufficiency of genes such as *SHOX*, plays a fundamental role in the development of key features like short stature and gonadal dysgenesis. Multidisciplinary management involving endocrinologists, cardiologists, nephrologists, psychologists, and other specialists is essential for optimizing health outcomes. As genetic and clinical understanding continues to evolve, early diagnosis and personalized care strategies will further enhance the quality of life for individuals with Turner syndrome.