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Editorial

Karyotype Based Multidisciplinary Approach in Adults with Turner Syndrome

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Background

Turner syndrome (TS) involves 45XO monosomy while TS variants are mostly 45XO/46XY or 45XO/46XX (with phenotype varying from female to male) [1-5]. Up to 30% of monosomy X cases are actually mosaicisms. [5,6] Specific gene mutations have been searched in order to explain the wide forms of clinical presentations. [4,5,7]. The most constant features are short stature and premature ovarian failure [5,7]. TS embrace a large area of medical and surgical specialties being regarded as the traditional disease involving a multidisciplinary team. The specialists familiar with specific anomalies in TS need a different approach in adult population compare to children. Some pathologies have different levels of risk if the monosomy is presented or not and thus new strategies are based on karyotype [8].

Multidisciplinary Approach

Genetic consult in adults is necessary if the confirmation was not obtained during childhood [3]. Current chromosome analysis of blood lymphocytes does not rule out low grade or gonad mosaicism thus the need of a secondary test as FISH (Fluorescence in situ hybridization) in case of 45XO/46XY or 45XO [6,9-11]. Y chromosome is positive in 5% of TS [10]. Some cases especially with XX mosaicism might have a mild phenotype so the diagnosis is delayed to adult years [1,3,4].

Gynecological (surgical) approach is needed in case of Y mosaicism because of gonadoblastoma risk (of 12-14% to 30%) that is exclusively found in this variant thus the need for genetic diagnosis regardless the patient's age [2,10-12]. Malignant transformation to dysgerminoma is correlated to TSPY gene that acts as oncogene only in dysgenetic gonads [10,13]**.** The laparoscopic gonadectomy is similar between pediatric and adult population except for the lack of general consensus regarding the simultaneous salpingectomy in children [14].

Cardiologic complications are the most important co-morbidities in adults with TS. The approach is different based on patients' age or potential pregnancy status but not on karyotype [8,15-18]. Two patterns are seen: congenital cardiovascular defects (as bicuspid aortic valve at 30% of TS, and coartaction of aorta at 12%) developing an increased the risk of dissection of aorta especially during pregnancy and arterial hypertension. Lifelong cardiac surveillance is necessary as well as new mathematical models of aortic dimensions in adults with short stature [8,15-18].

ORL involves conductive hear loss related to recurrent otitis media seen early in life, especially in monosomy cases and found as adult deafness and progressive sensori-neural hearing loss that usually starts during transitions to adult, and it cannot be anticipated except for a higher correlation to 45XO/46XX [19-21].

Gastroenterology has two major points: first the adults with TS might experience liver disease more frequent than general population and than previously was recognised regardless the karyotype and secondary an increased risk of celiac disease [5,22].

Renal involvement in adults with TS is represented by an increased risk of high blood pressure and recurrent urinary infections potential associated with congenital malformations but there are not consistent data to correlate with karyotype [23,24].

Some studies showed that mosaicism associates more frequent renal anomalies if XIAP (X-linked inhibitor of apoptosis protein) expression is abnormal [16].

Endocrine adult approach is focused on four major aspects: (I) ovarian insufficiency and related problems as therapy through the reproductive age and potential pregnancy, (II) bone health, (III) autoimmune thyroiditis, and (IV) diabetes mellitus.

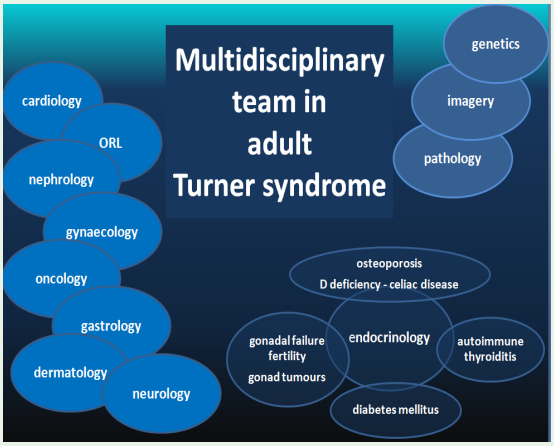

Figure 1: Multidisciplinary team in approaching adult Turner syndrome.

(I) Gonad failure is currently seen in TS. Spontaneous puberty is rarely found (10-30%) in patients with 45XO/46XX (or exceptional in 45XO/47XXX) and it goes to menarche in even less cases (5-10%) [5,25,26]. Estrogens replacement therapy is necessary for timing puberty, for archiving adequate substitution during adulthood equivalent to the reproductive years thought menopause (lower doses) [5]. Spontaneous pregnancy is achieved in 5% of TS (in 45XO/46XX) [26]. Recently a higher number of females obtain pregnancies by oocyte donation for assisted reproduction [5]. This comes together with an augmented cardiac risk [5,17,18,27] A potential alternative in obtaining a pregnancy is fertility preservation by taking a biopsy together with cryopreservation of primordial follicles from adolescents at risk of premature ovarian failure (especially with 45XO/46XX) that is best performed at 12-13 years but this is not currently used [28].

(II) The dwarfism does not associate an adult Growth Hormone (GH) deficiency syndrome thus the therapy with GH in adults is not necessary. However if the therapy was started before the growth cartilages are closed potential long distance effects might be seen in adults especially if higher doses have been used as generally it is recommended [5,27]. The gene anomaly behind short stature is SHOX (short stature homeobox-containing) and some connective tissue growth factor (Ctgf) disturbances have been revealed [3,5,7,29].

Vitamin D deficiency is frequently found among both children and adults with TS potentially correlated to celiac disease [30]. Vitamin D Receptor (VDR) gene polymorphisms (like BsmI and FokI) were found in correlations to the bone status [31]. Other studies showed that thyroid involvement is independent of VDR polymorphisms (as ApaI/G1025-49 or TaqI/T1056C) [32]. Also reduced bone strength is described when compared with healthy subjects revealing disturbances in bone-loading sensitivity [33].

The lack of estrogens has dramatic effects on bone mass and increases the bone turnover markers. If menses are presented so estrogens levels are adequate in 46XX variants these aspects are diminished [34]. Estrogens replacement at adolescents and adults significantly improve the trabecular Bone Mineral Density (BMD) [35]. SHOX gene also correlates with reduced cortical BMD (independently of mosaicism). This is not corrected under estrogens; bisphosphonates have limited effects while GH therapy during childhood helps bone mass achievement although not all the authors agree [4,11,36,37,38]. Central Dual-Energy X-ray Absortiometry might not be accurate in adults with a height less than 147 centimetres [37,38].

(III) Hashimoto thyroiditis is associated with TS (monosomy or mosaics) in a higher percent than general population; up to 50% of adults will have positive thyroid antibodies [39,40].

(IV) Diabetes mellitus is correlated to a higher risk of obese adults in TS regardless karyotype [41]. The insulin resistance is connected to liver steatosis and metabolic syndrome [42,43].

Conclusion

The general framework in adult TS is complex and multidisciplinary; gene mutations are continuously searched in order to explain the phenotype variety; recent data suggests an increased number of assisted fertility procedures and thus supplementary cardiac risks are involved; the prognosis is improved knowing the genetic backup and related clinical damage.

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