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Turner Syndrome

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Abstract

Turner syndrome (TS) is a neurogenetic disorder characterized by partial or complete monosomy-X. TS is associated with certain physical and medical features including estrogen deficiency, short stature and increased risk for several diseases with cardiac conditions being among the most serious. Girls with TS are typically treated with growth hormone and estrogen replacement therapies to address short stature and estrogen deficiency. The cognitive-behavioral phenotype associated with TS includes strengths in verbal domains with impairments in visual-spatial, executive function and emotion processing. Genetic analyses have identified the short stature homeobox (*SHOX*) gene as being a candidate gene for short stature and other skeletal abnormalities associated with TS but currently the gene or genes associated with cognitive impairments remain unknown. However, significant progress has been made in describing neurodevelopmental and neurobiologic factors underlying these impairments and potential interventions are on the horizon. Less is known regarding psychosocial and psychiatric functioning in TS but essential aspects of psychotherapeutic treatment plans are suggested in this report. Future investigations of TS should include continued genetic studies such as microarray analyses and determination of candidate genes for both physical and cognitive features. Multimodal, interdisciplinary studies will be essential for identifying optimal, syndrome-specific interventions for improving the lives of individuals with TS.

Keywords

Turner syndrome; X-monosomy; genetics; cognitive-behavioral; psychosocial

Turner syndrome (TS) is a complex phenotype associated with complete or partial monosomy of the X chromosome, usually the result of a sporadic chromosomal nondisjunction. TS is one of the most common sex chromosome abnormalities, affecting approximately 1 in 2,000 live born females [1–3]. The physical phenotype associated with TS includes short stature, ovarian failure, webbed neck, cardiac abnormalities, impaired glucose tolerance, thyroid disease and hearing loss [1,4–7]. There is considerable heterogeneity of phenotypic features, with short stature and gonadal dysgenesis being the most consistent [3]. Thus, a majority of females with TS are treated with growth hormone and estrogen replacement therapies [1].

Genetics

Karyotypes

As indicated above, TS is defined by a partially or completely absent X-chromosome. The majority (approximately 50%) of females with TS have a 45,X or *non-mosaic* karyotype [8, 9] Several karyotype variations exist including short or long arm deletion, ring X,

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isochromosome of the long arm (resulting in a fusion of chromosome arms) and mosaicism, a combination of cell lines such as 45,X and 46,XX [10]. Many reports indicate that mosaicism tends to moderate outcome [3,7] and studies show that physical features such as cardiovascular symptoms and gonadal dysfunction tend to vary in frequency across the different karyotypes [10]. It is currently unclear exactly how these various karyotypes differ in terms of cognitive-behavioral function.

Genotype-Phenotype Associations

In a typically developing female with a normal complement of 46 chromosomes, one of the X chromosomes is inactivated during early embryonic development, a phenomenon known as dosage compensation or lyonization [11,12]. This epigenetic mechanism functions to equalize the dosage of X-linked genes between females and males. However, several genes on the "inactive" X chromosome in females actually *escape* inactivation to at least some degree [13,14]. Therefore, TS might be considered the result of partial or complete absence of these genes that escape inactivation.

Genes that are potentially associated with aspects of the TS phenotype are thus likely to be those that escape X-inactivation and have functional homologues on the Y chromosome. One such gene is the short stature homeobox (*SHOX*) gene located on the pseudoautosomal region of the X-chromosome. *SHOX* has been identified as a candidate gene for short stature [15, 16] as well as for skeletal abnormalities associated with TS including high-arched palate, abnormal auricular development, cubitus valgus, genu valgum, Madelung deformity and short metacarpals [17]. Other candidate genes are currently under investigation.

Genomic Imprinting

Differential outcome stemming from genomic imprinting [18] is another genetic factor of interest in TS. Whether an imprinted gene is expressed depends on its parental origin [19,20] Although the issue remains controversial, a limited number of studies investigating imprinting effects in TS have demonstrated a possible influence on cognitive-behavioral phenotype. Individuals who retain the maternal X chromosome (X^m) may demonstrated greater impairments compared to those with the paternal X chromosome (X^p) [21–25]. Our laboratory demonstrated altered neurodevelopment in temporal and occipital regions in individuals with X^m compared to controls while those with X^p were not significantly different from controls [21,22]. Others have demonstrated no imprinting effects in cognitive performance [26] or neurodevelopment [27,28]. Some have observed individuals with X^p rather than X^m, to have poorer outcome [29]. The results of another study suggested that each parent-of-origin TS subgroup might be associated with a particular profile of deficits [30].

Physical abnormalities

The most common (i.e. frequency of 50% or greater) physical abnormalities affecting girls with TS include short stature, infertility, estrogen deficiency, hypertension, elevated hepatic enzymes, middle ear infection, micrognathia, bone age retardation, decreased bone mineral content, cubitus valgus, and poor thriving during the first postnatal year [1]. Females with TS also have significantly higher risks for certain diseases compared to the general population including hypothyroidism, diabetes, heart disease, osteoporosis, congenital malformations (heart, urinary system, face, neck, ears), neurovascular disease and cirrhosis of the liver as well as colon and rectal cancers [1].

Cardiac abnormalities are considered the most serious medical problems associated with TS. There exists a high rate of morbidity among the TS population, primarily due to congenital and acquired heart conditions such as coarctation of the aorta, biscuspid aortic valves, mitral valve prolapse, hypertension, ischemic heart disease and arteriosclerosis [1,4,31–33].

Cognitive Phenotype

Visual-Spatial Skills

Individuals with TS typically demonstrate normal global intellectual functioning; however, nonverbal abilities are often significantly impaired [7,34,35]. An uneven cognitive profile with verbal skills tending to be significantly higher than nonverbal skills is often considered to be the hallmark of cognitive ability in TS. Females with TS have been shown to demonstrate intact if not superior language development compared to controls. For example, studies have shown higher reading levels, accuracy, and comprehension in participants with TS compared with age-matched typically developing controls [36]. Individuals with TS also have been shown to have better receptive vocabulary skills and understand significantly more low-frequency (less common) words than controls [37]. However, one study of girls with TS indicated poorer ability in word retrieval and non-lexical reading in conjunction with preserved performance in irregular word reading, phoneme analysis and letter fluency compared to controls [38]. In contrast, girls with TS are at high risk for developing deficits in visual-spatial, visual-perceptual and visual-constructional abilities [39–42]. Specifically, females with TS tend to demonstrate significant deficits on tests of mental rotation, object assembly and face recognition but perform comparably to controls on visual sequential memory and block span tests [38] Deficits on visual-spatial tasks often include right-left disorientation and difficulty with design copying as well as an executive function component with poor planning and organization [43–48]. Cornoldi et al. suggested that while TS may be associated with general visual-spatial deficits, individual differences in specific performance patterns may exist [49]. Visual-spatial impairments tend to be resistant to estrogen and androgen-replacement therapies [35,40] suggesting that this characteristic may be independent of hormone effects and require a more precise intervention. Visual-spatial skills are known to be associated primarily with parietal-occipital pathways [50–52] Neuroimaging studies suggest that parietal-occipital metabolism and morphology are abnormal in individuals with TS compared with healthy controls. [21, 53–59]. We additionally showed that these volumetric differences may be specific to the superior parietal lobule and the postcentral gyrus, regions are associated with visual-spatial function, visuomotor learning and spatial working memory [53]

Executive Skills

Although not reported as frequently as visual-spatial deficits, impaired executive function also has been observed in individuals with TS. Problems with executive skills associated with TS may include impaired attention and concentration, problem-solving ability, organization, working memory, behavioral control and use of goal-directed strategies, as well as increased impulsivity and slower processing speed [29,35,46,60–62]. TS also may be associated with increased risk for Attention Deficit Hyperactivity Disorder (ADHD) [63]; Russell and colleagues reported an 18-fold increased prevalence in TS compared to controls [26]. Several studies have demonstrated abnormal brain activation patterns in prefrontal-striatal pathways associated with executive task performance in girls with TS [43,64,65].

Connectivity of Visual-Spatial and Executive Functions

We have illustrated that participants with TS tend to perform comparably to controls during easier tasks but fail when task demands are increased. Brain activation in frontal-parietal regions tends to be increased compared to controls during easier tasks but reduced during more difficult tasks [43,66]. However, when there is no spatial component, girls with TS perform similarly to controls on executive tasks and tend to show increased prefrontal activation [67].

These data suggest that while executive tasks in general may be more effortful for individuals with TS, they may be able to compensate for this weakness to some degree by recruiting additional prefrontal resources. However, they seem to be unable to successfully engage

alternate or additional systems when there is a spatial component, particularly during more difficult tasks. This profile of spatial executive deficits could be explained by a number of factors including aberrant neurodevelopment in both the parietal and frontal lobes and/or an impairment in frontal-parietal connectivity. Supporting this possibility, we demonstrated significantly reduced white matter integrity in parietal-frontal pathways [68].

We also examined functional connectivity in females with TS using functional MRI (fMRI) results from three tasks that are known to engage frontal-parietal systems. Functional connectivity analyses provide insight into regions that are likely connected within functional networks [69]. We found that activation in the parietal regions was *negatively* correlated with frontal activation in girls with TS during all three tasks. Controls on the other hand, demonstrated *positive* correlations between parietal and frontal regions during the three tasks [70]. These findings suggest that the *interaction* between parietal and frontal lobe systems may provide a more precise explanation for spatial-executive deficits in TS than independent parietal and/or frontal lobe impairments.

In fact, many of the cognitive impairments noted among individuals with TS may reflect similar problems with integrating relevant neural systems. For example, TS has been associated with difficulties in integration of details into a gestalt and global versus local deficits [71]. Additionally, individuals with TS appear to be at risk for difficulties with arithmetic [56,57, 72,73] and spatial memory [30,35,74,75]. These abilities rely partly on integration of visual-spatial and executive functioning. Focusing on the integration of cognitive systems in TS might suggest directions for intervention. For example, cognitive remediation programs should include exercises that strengthen connection of systems (e.g. visual-spatial-executive) rather than independent functions (visual-spatial only).

Psychosocial Functioning

Impairments in social functioning have been noted among individuals with TS. Adolescent girls with TS are at greater risk for having problems related to lower social activity, poor social coping skills and increased immaturity, hyperactivity and impulsivity compared to their peers [63]. Girls with TS may have more difficulties maintaining relationships, relating to others, have fewer friends and tend to be more socially isolated than controls [76]. Social difficulties in girls with TS may partially stem from impairments in face and emotion processing as well as interpreting gaze in individuals with TS [77–81]. Some researchers have suggested that a diagnosis of autism, a neurodevelopmental disorder characterized by social deficits, is more common among girls with TS [25,82,83] but this remains controversial.

Because the amygdala is known to be involved in recognition of facial emotion and social judgment [84], neuroimaging studies have investigated amygdala development associated with TS. Good and colleagues showed that females with Turner syndrome have significantly enlarged amygdala volumes compared to female and male control participants [27]. Our laboratory confirmed enlarged amygdala volumes associated with TS using a different but complementary neuroimaging method [28].

An fMRI study demonstrated enhanced right amygdala activation to fearful faces in individuals with TS compared to controls. Amygdala activation in controls tended to peak initially and then decrease over time whereas in females with TS, activation persisted with little change in magnitude. Additionally, performance on a facial emotion recognition task was correlated with amygdala and fusiform activation in the control but not the TS group. Functional co-activation between the amygdala and fusiform was decreased in the TS group compared to controls. The authors suggested that impaired appraisal of facial affect and habituation to fearful stimuli may stem from impaired functional connectivity between these structures in the TS group [85].

Studies of TS also have shown aberrant neurodevelopment in the orbitofrontal cortex and superior temporal sulcus, additional regions involved in social cognition and face processing [27,55,57]. Some researchers believe that social skills deficits in TS stemmed largely from visual-spatial, nonverbal impairments similar to the cognitive-behavioral profile associated with Nonverbal Learning Disorder [71,86]. However, the above neuroimaging studies suggest that psychosocial functioning in TS may be independent of visual-spatial skills deficits. Specifically, deficits in amygdala function but not posterior visual-spatial processing systems were observed in association with facial emotion processing tasks. Skuse and colleagues argue that social cognition performance in TS is not strongly correlated with visual-spatial ability and that nonverbal deficits cannot adequately explain the findings that individuals with TS tend to show greater impairment for fearful stimuli [24,77,78] A primary nonverbal deficit would seem to affect appraisal of all facial emotions similarly. This is an area of functioning in TS that requires further investigation.

Psychiatric Disorders

Shyness, anxiety, low self-esteem and depression, frequently linked to self-consciousness over physical appearance and/or infertility, have been described in studies of TS. However, psychiatric functioning remains an area of limited and conflicting information in TS, requiring further study. In a study of 100 individuals with TS, age 16–61, Schmidt and colleagues used 4 rating scales and noted significantly higher anxiety, shyness and depression as well as lower self-esteem compared to controls. These findings were irrespective of factors such as age, education and marital status [87]. Girls with TS age 9–17 demonstrated lower self-esteem and higher levels of state anxiety than controls using different self-report measures [88] Keysor et al. reported that individuals with TS age 12–22 showed heightened physiological arousal, including skin conductance, heart rate and gastrocnemius EMG, during certain cognitive tasks [89]. A recent study indicated that low self-esteem and poor social adjustment are associated with delayed or absent sexual relationship experiences [90] Whereas many reports have suggested height, physical appearance and/or infertility as underlying factors in low self-esteem, Carel and colleagues demonstrated that hearing loss, socioeconomic status and cardiac problems also may contribute to impaired social adjustment [90].

Another group noted lower self-perception and bodily attitude but no evidence of depression in 50 females with TS (mean age 18 + 0.3) who completed self-report scales [91] One study that included self-report and parental ratings indicated that girls with TS age 6–22 were not significantly more anxious than controls [92]. A large study involving 100 women with TS age 16–61 utilizing a structured diagnostic interview indicated that lifetime incidence of mood disorders, but not anxiety, was twice as high as community based samples. However, current and lifetime prevalence of psychiatric syndromes including mood and anxiety disorders was not substantially higher in TS than that of individuals in medical outpatient or gynecological clinics. This suggests that mood disturbance in TS is not likely specific to TS but rather increased due to medical problems in general [93].

Treatment

Growth Hormone

As indicated previously, one of the most common clinical features among individuals with TS is short stature which can affect peer relationships and social adjustment. Growth hormone (GH) is typically prescribed to children with TS in order to increase final height. Girls with TS who were treated with GH for one year were significantly taller than those who did not receive GH [94]. Studies suggest that GH treatment can result in achievement of normal adult height, and starting GH at an early age (4–6 years) appears to be a factor in the success of the treatment [1,95,96]. The effects of GH on height can diminish after the first 1–2 years of administration

and therefore an escalating dosage schedule is often required, with higher doses in adolescence [1,97].

Some clinicians have expressed concerns that GH treatment may result in undesirable changes to body proportions such as enlarged feet and hands in adolescents [1]. Further research is needed in this area. Researchers also warn treatment providers to be wary of psychosocial problems related to weight management issues in TS [98]. However, GH treatment may result in increased lean body mass and decreased body fat thus improving physical health associated with body composition [94,96].

GH does not affect bone mineral density [94] but may increase the risk of otitis media and certain joint disorders [1]. There also some concerns regarding increased risk of colon and lymphatic cancers [97]. GH decreases insulin sensitivity which, in combination with a tendency towards greater adiposity in TS, may contribute to development of type 2 diabetes [99]. However, insulin resistance tends to decrease after approximately 7–8 years of GH therapy and returns to normal after GH therapy is discontinued [100].

It is unclear whether or not GH therapy affects cognitive function in girls with TS. Very few studies examining this relationship have been conducted. One small (N = 20) but very well designed study indicated no influence of GH on cognitive function in females with TS. [101]. A follow-up study employing an expanded cognitive testing battery confirmed these findings [14].

Estrogen Replacement Therapy

One of the key features of TS is estrogen deficiency [102] that occurs secondary to ovarian dysgenesis or degeneration associated with early follicular apoptosis [1]. Despite ovarian abnormality being one of the most common features of TS [1], approximately 5–10% of females with TS demonstrate some degree of spontaneous puberty and 2–7% experience spontaneous pregnancy [103]. These pregnancies tend to be at high risk for miscarriages, genetic abnormalities, stillbirths and malformations [103] However, there have been some rare reports of successful, uneventful pregnancies in women with TS [103,104].

Estrogen replacement therapy (ERT) is currently the standard treatment for estrogen deficiency/insufficiency. ERT should ideally be started around the age of 12 or at an age consistent with pubertal development in the patient's peers to decrease psychosocial distress [1] ERT should be initiated also with consideration of GH therapy. Some reports have indicated that ERT can reduce final adult height in patients being treated with GH [105,106] However, more recent studies indicate that the use of transdermal or intramuscular estradiol administration [106] and/or initial use of a low-dose parenteral estradiol with an increasing dosage schedule [91,107,108] may reduce ERT's affect on height attainment.

It has been suggested that some features of cognitive impairment associated with TS may be related to estrogen function [101,109]. Certain cognitive deficits such as motor speed, nonverbal processing time, verbal and nonverbal memory may improve following ERT [62, 110]. Many other areas of cognitive function, particularly those associated with visual-spatial and visual-motor processing as well as attention, seem to persist despite ERT [35]. ERT has been shown to have several beneficial effects including age-appropriate development of secondary sexual characteristics, improved psychosocial functioning, increased bone mineral density and better uterine development [111].

Girls with TS also demonstrate androgen deficiency [102]. Androgens are believed to have a significant role in cognitive function, potentially enhancing cognitive performance and emotional state [112] One study showed that oxandrolone (synthesized testosterone) may help

improve certain cognitive functions such as working memory performance in girls with TS [40]. Further studies are required to determine if androgen replacement is an efficacious treatment for cognitive impairments associated with TS.

Psychosocial

There have been very limited studies of psychosocial treatment efficacy in TS. Existing studies are outdated and tend to involve case studies rather than randomized clinical trials or other more robust methods [113–115]. The paucity of literature in this area reflects our currently limited understanding of psychiatric functioning in TS. Emotional difficulties may stem primarily from chronic medical problems and social isolation rather than X-monosomy.

It is hoped that continuing to more precisely define the cognitive, psychosocial, neurobiologic, endocrinological, genetic and other relevant aspects of TS will aid in developing more syndrome-specific psychosocial interventions. Based on our understanding of TS thus far, such interventions should ideally include a combination of the following, based on individual strengths and weaknesses: 1) general coping and adaptive skills training as well as a specific focus on dealing with chronic medical problems such as cardiovascular disease, hearing impairment and infertility; 2) social skills training including self-monitoring, social perspective taking, facial affect and body language recognition and interpretation as well as group social skills therapy; 3) stress management training to help prevent and treat anxiety and mood disturbances; 4) emphasis on improving self-esteem and self-perception; and 5) internal and external strategies to compensate for cognitive weaknesses such as using self-talk to pay attention and remain on task, focusing on doing one task correctly, rather than doing several things at once and paraphrasing what others have said to ensure comprehension.

Treatment plans should consider the individual's cognitive profile. Neuropsychological assessments can be vitally helpful in informing education and special education services as well as psychotherapy parameters. For example, a girl with TS who has executive function deficits such as abstract reasoning or attention impairments is more likely to benefit from concrete, behaviorally oriented therapies rather than psychoanalytic ones.

Summary and Future Directions

Significant progress has been made in describing the cognitive-behavioral, neurobiologic, endocrinologic, physical and genetic factors associated with Turner syndrome. However, many questions remain. Existing studies have typically involved relatively small sample sizes, large age ranges and mixed genotypes. Smaller sample sizes obviously present potential difficulties in terms of power and generalizability. Large age ranges limit the ability to determine how hormone replacement therapies, particularly estrogen treatments, impact outcome in TS. Additionally, there have been no studies on gene expression patterns of girls with X monosomy and TS. Studies involving genetic analyses such as microarray technology will be necessary to examine gene expression profiles in girls with TS and identify potential candidate genes underlying the cognitive-behavioral impairments associated with TS. Continued studies of X-linked genes that escape inactivation and have Y chromosome homologues also will be essential in identifying candidate genes involved in the cognitive-behavioral and physical phenotypes of TS.

Genetic profiles of participants, including genotype, karyotype and genomic parental origin are of particular interest for future studies of TS. Because individuals with the maternal X chromosome outnumber those with the paternal X by approximately 2:1 [116,117], further studies are required that oversample for participants with X^p Also, many studies tend to include only females with a monosomic 45,X genotype (non-mosaic). To date, there has not been a comprehensive study of the cognitive-behavioral features associated with various karyotypes

in TS. The analyses involved in interpreting cognitive-behavioral outcome associated with cytogenetic variants are quite complex due to the large number of variants that exist. However, these studies would offer a unique opportunity to investigate the relationship between X chromosome gene function and cognitive-behavioral phenotype. Future studies could begin including individuals with mosaic TS genotypes and compare their outcome to those with a non-mosaic genotype.

Finally, cross-modal, longitudinal, randomized clinical trial and other such comprehensive study designs are needed to start examining the relationships between aspects of TS such as neurodevelopment, endocrine function, medical status and cognitive outcome. These studies will hopefully aid us in developing syndrome specific interventions that will improve functioning and quality of life in individuals with TS.

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