

Adult women with Turner syndrome: A systematic evaluation of current and past psychiatric illness, social functioning, and self-esteem

Peter J. Schmidt^{a,*}, David R. Rubinow^a, Carolyn A. Bondy^b

^a Behavioral Endocrinology Branch, National Institute of Mental Health,

Department of Health and Human Services, Bethesda MD 20892-1276, United States

^b Developmental Endocrinology Branch, National Institute of Child Health and Human Development,

Department of Health and Human Services, Bethesda MD 20892-1276, United States

Abstract. Abnormalities in both quality of life and cognitive measures have been well-documented in women with Turner Syndrome (TS). Additionally, shyness and social anxiety appear to be common clinical features of TS. However, few studies have systematically examined the presence of mood and behavior syndromes in these women. In this chapter we report our recent studies on the psychological and social aspects of Turner syndrome in adult women. Overall, rates of psychiatric syndromes were not higher in women with TS than in women attending gynecologic clinics. Nonetheless, premature ovarian failure was associated with depression, reduced self-esteem and impaired social functioning. Elucidation of the specific mechanisms of this effect and identification of the women at particular risk are important areas for further study. Attention to psychological health and social functioning should be an important part of the care for women with premature ovarian failure, regardless of the underlying disorder. Published by Elsevier B.V.

Keywords: Turner syndrome; Depression; Mood disorder; Shyness

1. Introduction

Turner Syndrome (TS) is associated with alterations in the development and function of numerous physiologic systems including the brain [1]. Recent neuroimaging studies report both anatomical and functional differences between girls or women with TS and age-matched controls [2–6]. Many of these same brain regions serve important roles in the regulation of

* Corresponding author. NIMH, Building 10-CRC, Room 65340, 10 Center Dr. MSC1276, Bethesda MD 20892-1276. Tel.: +1 301 496 6120; fax: +1 301 4022588.

E-mail address: peterschmidt@mail.nih.gov (P.J. Schmidt).

cognitive processes, social behavior, and affective state. Indeed, both girls and women with TS demonstrate a distinct neurocognitive profile where verbal ability is generally normal while visual–spatial abilities, working memory and executive function may be impaired.

While specific cognitive deficits have been documented in TS, the prevalence of psychopathology in this disorder has only been addressed in a few small studies. Clinical observations suggest that many girls with TS exhibit immaturity, poor self-esteem and difficulties with social relationships [7–16]. Some investigators associate social difficulties in TS to the non-verbal learning disability [8], while others view them as neurobiologically-based deficits in “social cognition” associated with difficulties in recognizing facial expression or gaze direction [17]. Whether these psychological features observed in girls with TS portend an increased risk of psychiatric diagnoses in adult life is unclear.

This chapter reviews our recent studies on DSM-IV psychiatric disorders in women with TS [18], and on the potential role of premature ovarian failure in symptoms of shyness, social anxiety, and low self esteem in women with TS [19].

1.1. Prevalence of Axis I and II psychiatric illness

Three previous studies have evaluated the presence of psychiatric diagnoses in women with TS. Delooz et al. [9] administered a structured diagnostic interview to 20 women with TS and observed rates of lifetime psychiatric illness of 50% (the majority of which were mood disorders) and current mood disorders of 20%. Two other studies reported both lower and higher rates of psychiatric illness, respectively. McCauley et al. observed a 22% lifetime prevalence of psychiatric illness in a sample of 27 women with TS [7]. In contrast, Downey et al. administered a structured diagnostic interview to 23 women with TS drawn from their private practice and reported a 70% lifetime prevalence of psychiatric illness [10]. However, the higher rate of lifetime psychiatric illness observed by Downey et al. may reflect the selection of women with more severe mood and behavioral symptoms present in this practice. In our recent study, one hundred TS women [18] were evaluated with the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (fourth edition) (SCID I and II) [20], a structured diagnostic interview that establishes the presence or absence of Axis I and II diagnoses.

Forty-eight percent of women did not meet criteria for any current or past Axis I psychiatric diagnosis, and only five women met criteria for an Axis II (i.e., personality disorders) diagnosis (three of whom also met criteria for an Axis I condition) (Table 1). Eighteen percent of women with TS met criteria for a **current** Axis I diagnosis: 11% affective disorders (mainly major depression (5%), minor depression (5%) and dysthymia (1%)), and 11% anxiety disorders. Depressive and anxiety disorders coexisted in four women. Comparable rates of **current** Axis I diagnoses from community-based and gynecology clinic-based samples of women are listed in Table 1.

Lifetime major depression (defined as the occurrence of a major depression at any time [current or past] in the woman’s life) occurred in 36% of women, and lifetime affective disorders (any mood disorder) in 47% of women, compared with rates in the community of 20% and 24%, respectively (as well as 63% in one gynecology clinic-based study [21]). Lifetime histories of anxiety disorders were observed in 15% of women with TS and in 15–30% of women in community studies.

Table 1
 Axes I and II diagnoses in women with Turner Syndrome ($n=100$)

	Current psychiatric Diagnosis ($n=18$)	Past psychiatry Diagnosis ($n=46$) ^a
Affective disorders	11 (7%) ^b	44
Major depression	5 (3–6%) [6%]	33
Minor depression	5	8
Dysthymia	1	0
Bipolar disorder	0	3
Anxiety disorders	11 (10%) [7%]	7
Panic disorder	4	1
Social phobia	2 (1–4%)	0
Generalized anxiety disorder	2	0
Specific phobia	2	1
Anxiety disorder NOS	1	0
PTSD	0	5
Eating disorder	0	6
Anorexia	0	5
Bulimia	0	1
Substance dependence	0	3
Axis II diagnosis	5	
Avoidant	2	
Borderline	1	
Obsessive	2	

Women with both a current and past Axis I diagnoses are listed separately under each section.

^a 46% of women with TS did not meet SCID criteria for current or past Axis I or II psychiatric diagnosis.

^b Published rates of current Axis I diagnosis appear in rounded parentheses () from community samples and in square parentheses [] from gynecology clinic samples [22,24–26].

Comparison between TS women with and without lifetime affective disorders showed no differences in the presence of webbing of the neck (Chi-square=0.08, $p=NS$), history of treatment with GH (Chi-square=0.9, $p=NS$), and current treatment with thyroid hormone (Chi-square=0.9, $p=NS$). Additionally, height did not significantly differ in those women with and without an affective disorder (Student's $t_{99}=0.2$, $p=NS$).

In this study, the number of women with TS who met criteria for a current Axis I psychiatric illness was comparable to reported rates of women in several community-based [22–24] and gynecology clinic-based [21,25] samples. Specifically, rates of current mood and anxiety disorders were not substantially increased in women with TS despite discontinuing hormone replacement therapy for the 2 weeks prior to the interview. The rate of **lifetime** psychiatric diagnoses was almost twice as high in women with TS compared to community-based samples and reflected a higher rate of mood but not anxiety disorders in these women. However, both the current and lifetime rates of mood disorders were not substantially higher than those previously reported in either medical outpatient [26,27] or gynecology clinics [21]. Thus, our data would suggest that TS is not associated with an increased risk of depressive illness, beyond that expected to occur in association with any medical or gynecologic condition.

Similarly, despite possible associations between mood symptoms and the physical stigmata of TS, the presence of a webbing of the neck or short stature was not disproportionately

represented in the women with mood disorders. Finally, our data did not suggest a difference in the risks for psychiatric disorders in those TS women with 45X compared to those with other karyotype abnormalities, including mosaic patterns.

This study was the largest case series focusing on the psychiatric status of women with TS. Our major finding was that women with TS do not report substantially higher rates of current psychiatric disorders including depression or anxiety disorders, compared to published community-based prevalence rates. A higher lifetime rate of mood disorders (but not psychiatric disorders in general) was observed in women with TS compared to that reported in community-based samples, but comparable to that observed in gynecology clinic-based samples.

1.2. Shyness, social anxiety and self-esteem

Clinical reports have documented that girls with TS experience more social anxiety and shyness than matched controls [28], traits proposed to be on a continuum with some anxiety disorders such as social phobia. Additionally, women with TS have been observed to display deficits in several social processes including recognizing facial expressions and determining the direction of eye gaze. Finally, both structural and functional neuroimaging studies have identified alterations in several brain regions associated with social cognition and behavior [29,30] in women with TS compared to controls including the amygdala, superior temporal sulcus, and orbitofrontal cortex.

These observations concerning the social difficulties in TS have been based mainly on studies in pediatric populations, when dealing with short stature and learning difficulties is paramount. For adults with TS, however, short stature or learning difficulties may not be major issues, while dealing with the experience of ovarian failure and infertility may come to the fore [10,31,32]. Premature ovarian failure could affect psychosocial functioning in at least two ways. Hormonal deficiency might impact brain regions involved in affect regulation and social behavior, potentially causing depression and social anxiety. In addition, experiential factors associated with loss of fertility may impact a woman's self-concept and perception of her role in relationships.

Previous studies on psychological aspects of TS have relied upon normative data or age-matched females with normal ovarian function as controls [7,33,34]. Since these groups differ significantly in height, neurobiological and ovarian function, it has not been possible to distinguish the role of these different factors in shaping the self-concept and social experiences of women with TS. To address this issue, we compared several specific measures of psychological function, with emphasis on feelings about social interactions, in women with TS and in women with spontaneous, karyotypically normal premature ovarian failure (POF), as well as normal controls. Women with TS and POF are similar in that both groups have a clear diagnosis of primary ovary failure, resulting in reduced sex steroids and infertility, at a relatively young age. They are dissimilar in that women with POF have a normal 46,XX karyotype, are of normal height and appearance and exhibit normal cognitive function [35]. Thus we evaluated two groups that differ in several respects but shared the diagnosis of premature ovarian failure.

The diagnosis of POF was based on at least 4 months of non-iatrogenic amenorrhea occurring in women less than 40 years, with at least two determinations of FSH levels

>40 mIU/ml, and a normal, 46,XX 50-cell peripheral karyotype. Both TS and POF women were routinely on estrogen/progestin hormone treatment, but discontinued hormone use approximately 2 weeks prior to study.

We also recruited a comparison group of 35 normal control women who were at least 18 years old, medication free, had normal menstrual cycles between 21 and 35 days, no current or past psychiatric diagnosis confirmed by a structured diagnostic interview [20], and had the absence of any medical condition confirmed by history, physical exam and laboratory testing.

Participants completed the following standardized cross-sectional symptom rating scales previously validated in community samples: (1) The Revised Shyness Scale [36] evaluating characteristics of shyness in different situations. Previous studies have found scores of 35 or above to be indicative of clinically significant shyness [37]. (2) The Social Anxiety Scale [38] measuring social anxiety and avoidance, with a higher score reflecting more severe social anxiety. (3) Rosenberg's Self Esteem Scale [39] assessing level of self esteem, with a higher score reflecting greater self-esteem. Additionally, to evaluate current mood symptoms each subject completed the Center for Epidemiologic Studies Depression Scale [40] (CES-D), a self-rated scale measuring severity of depressive symptoms.

Since the groups differed somewhat in age, this factor was used as a covariate in ANOVA between groups. Both women with TS and POF had significantly higher scores on the Shyness, Social Anxiety, and CES-D rating scales and significantly lower scores on the Self-Esteem Scale compared with normal controls (Fig. 1). Forty-six percent and 34% of women with TS and POF, respectively, were above the score indicative of clinically significant symptoms on the Shyness Scale [37] (35 point cut-off; Chi square=3.0, $p=0.08$).

Several factors could impact psychological outcomes in TS, aside from ovarian failure. There was a small effect of height in the TS group, which was negatively correlated with social anxiety ($R^2=0.05$, $p=0.03$) and positively with self-esteem ($R^2=0.06$, $p=0.02$). A major reason for using growth hormone to augment height in girls with TS is to improve their self-image and social functioning, but scores on psychological tests were no different in those that received growth hormone therapy vs. those that did not. Likewise, IQ scores and years of education were not correlated with these ratings. The presence of neck webbing is a cosmetic problem affecting ~ 30–40% of women with TS that might be expected to contribute to social stigmatization and thus psychosocial symptoms. However, symptom scores were not worse in the group with neck webbing vs. those without. Finally, test scores in the TS subgroup with a 45,X karyotype ($n=67$) were not significantly different from the subgroup with mosaic and partial deletion karyotypes ($n=33$, data not shown).

Our study demonstrated that young women with karyotypically normal premature ovarian failure and TS experience very similar psychosocial profiles characterized by increased shyness, social anxiety and depression, and decreased self-esteem compared to control women with normal ovarian function. Given major differences in genotype and phenotype between our two ovarian failure groups, the similarity in their responses to the psychological tests is striking. Women with TS were on average very short, while the women with POF were normal in height. The only commonality between these two groups was the shared experience of premature ovarian failure, indicating that this diagnosis has a distinct impact on psychosocial functioning.

The women with ovarian failure in this study routinely took estrogen and progestin therapy, so that chronic deficiency in these hormones seems unlikely to explain the

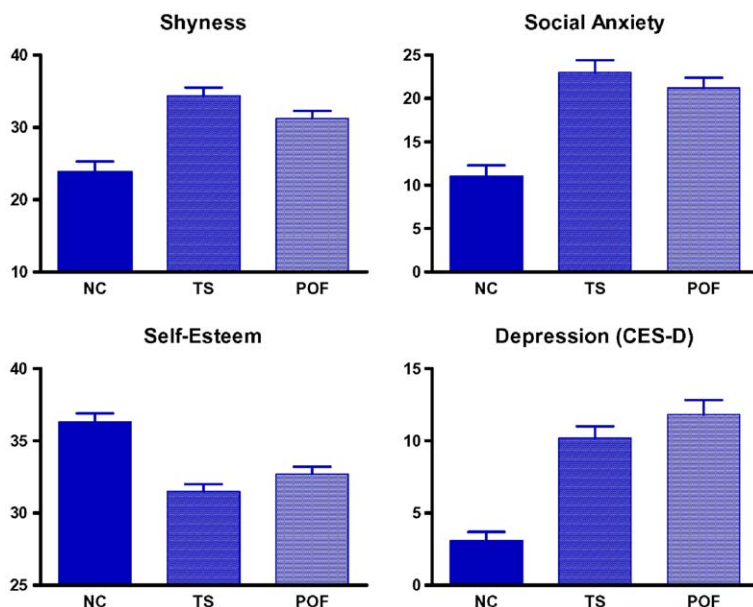


Fig. 1. High levels of shyness, social anxiety and depression (CES-D) and reduced self-esteem in women with TS and POF compared to women with normal ovarian function. The solid bars represent normal controls, the diagonal hatched bars — TS and the pixelated bars — POF. Data are means with SEM.

psychological distress reported here. Short-term withdrawal of estrogen/progestin treatment is not known to cause shyness, social anxiety or reduced self esteem, and depression scores and self esteem scores were actually worse in a POF group studied while on hormone treatment [41]. We found, in addition, that visual–spatial and perceptual difficulties did not correlate with any aspects of psychosocial dysfunction, suggesting that the shyness and social anxiety experienced by adults with TS are not related to neurocognitive deficits due to X-chromosome deletion. Supporting this view, women with POF have none of the perceptual deficits typically seen in TS [35], but nevertheless expressed the same range of emotional responses. The similar responses of women with TS and with POF on measures of shyness, social anxiety, self-esteem and depression suggest that the common experience of ovarian failure is the major determinant in their psychosocial phenotype. Short stature and dysmorphic features such as webbing of the neck are often thought to contribute to poor self-esteem in children with TS [16]. Approximately 40% of the women with TS had webbing of the neck, but this feature was not associated with any negative psychological symptoms. Short stature did contribute to reduced self-esteem and increased social anxiety and shyness among women with TS; although the effect was small, it could well account for the trend for worse scores on these scales in the TS group compared with the POF group. This finding is consistent with a recent observation in a large number of young women with TS that height and height gain from growth hormone treatment were not significantly associated with any quality of life dimensions [42].

These observations suggest that factors other than prolonged exposure to low levels of gonadal steroids, core neurobiological abnormalities, or physical appearance cause the shyness and social anxiety affecting many young women with ovarian failure. While it might be expected that loss of reproductive potential may cause depression and loss of self-esteem, this has not actually been established in an evidence-based study. These data, therefore, provide the first systematic and quantitative insight into the psychological impact of ovarian failure in young women, and is the first demonstration of a distinct social component to the psychological impact of this diagnosis.

2. Conclusions

The present findings represent the largest sample of adult women with TS to be evaluated with structured diagnostic interviews and standardized symptom rating scales. Our findings may differ from a population-based study on TS, since many of the women were self-referred, and our samples may have been a healthier, more motivated and less shy group of women. Nonetheless, the comparable rates of psychiatric conditions in this large sample of women to those published prevalence rates in gynecology clinics suggests that the neurobiologic and genetic abnormalities in TS do not uniquely or uniformly lead to psychiatric syndromes nor excessive shyness. Finally, our findings provide a unique picture of the psychosocial impact of a clearly established diagnosis of premature ovarian failure.

References

- [1] B. Lippe, Turner syndrome, *Endocrinol. Metab. Clin. N. Am.* 20 (1991) 121–152.
- [2] D.G.M. Murphy, et al., X-chromosome effects on female brain: a magnetic resonance imaging study of Turner's syndrome, *Lancet* 342 (1993) 1197–1200.
- [3] A.L. Reiss, et al., The effects of X monosomy on brain development: monozygotic twins discordant for Turner's syndrome, *Ann. Neurol.* 34 (1993) 95–107.
- [4] C. Rae, et al., Enlarged temporal lobes in Turner syndrome: an X-chromosome effect? *Cereb. Cortex* 14 (2004) 156–164.
- [5] C.D. Good, et al., Dosage-sensitive X-linked locus influences the development of amygdala and orbitofrontal cortex, and fear recognition in humans, *Brain* 126 (2003) 2431–2446.
- [6] S.R. Kesler, et al., Effects of X-monosomy and X-linked imprinting on superior temporal gyrus morphology in Turner syndrome, *Biol. Psychiatry* 54 (2003) 636–646.
- [7] E. McCauley, V.P. Sybert, A.A. Eurhardt, Psychosocial adjustment of adult women with Turner syndrome, *Clin. Genet.* 29 (1986) 284–290.
- [8] E. McCauley, et al., The Turner syndrome: cognitive deficits, affective discrimination, and behavior problems, *Child Dev.* 58 (1987) 464–473.
- [9] J. Deloos, et al., Turner syndrome patients as adults: a study of their cognitive profile, psychosocial functioning and psychopathological findings, *Genet. Couns.* 4 (1993) 169–179.
- [10] J. Downey, et al., Psychopathology and social functioning in women with Turner syndrome, *J. Nerv. Ment. Dis.* 177 (1989) 191–201.
- [11] E. McCauley, et al., Psychosocial development in adolescents with Turner syndrome, *J. Dev. Behav. Pediatr.* 22 (2001) 360–365.
- [12] E. McCauley, J. Ito, T. Kay, Psychosocial functioning in girls with Turner's syndrome and short stature: social skills, behavior problems, and self-concept, *J. Am. Acad. Child Psych.* 25 (1986) 105–112.
- [13] E. McCauley, et al., Self-esteem and behavior in girls with Turner syndrome, *J. Dev. Behav. Pediatr.* 16 (1995) 82–88.
- [14] B.F. Pennington, et al., The neuropsychological phenotype in Turner syndrome, *Cortex* 21 (1985) 391–404.

- [15] A. Swillen, et al., Intelligence, behaviour and psychosocial development in Turner syndrome. A cross-sectional study of 50 pre-adolescent and adolescent girls (4–20 years), *Genet. Couns.* 4 (1993) 7–18.
- [16] V.I. Rickert, et al., The effects of peer ridicule on depression and self-image among adolescent females with Turner syndrome, *J. Adolesc. Health* 19 (1996) 34–38.
- [17] D.H. Skuse, X-linked genes and mental functioning, *Hum. Mol. Genet.* 14 (2005) R27–R32.
- [18] G. Cardoso, et al., Current and lifetime psychiatric illness in women with Turner syndrome, *Gynecol. Endocrinol.* 19 (2004) 313–319.
- [19] P.J. Schmidt, et al., Shyness, social anxiety, and impaired self-esteem in Turner syndrome and premature ovarian failure, *JAMA* 295 (2006) 1374–1376.
- [20] M.B. First, et al., Structured clinical interview for DSM-IV axis I disorders — patient edition, Biometrics Research Department, New York State Psychiatric Institute, New York, N.Y., 1996
- [21] A.G. Hay, J. Bancroft, E.C. Johnstone, Affective symptoms in women attending a menopause clinic, *Br. J. Psychiatry* 164 (1994) 513–516.
- [22] M.M. Weissman, J.K. Myers, Affective disorders in a US urban community: the use of research diagnostic criteria in an epidemiological survey, *Arch. Gen. Psychiatry* 35 (1978) 1304–1311.
- [23] J. Angst, A. Dobler-Mikola, Do the diagnostic criteria determine the sex ratio in depression? *J. Affect. Disord.* 7 (1984) 189–198.
- [24] R.C. Kessler, et al., Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey, *Arch. Gen. Psychiatry* 51 (1994) 8–19.
- [25] R.L. Spitzer, et al., Validity and utility of the PRIME-MD patient health questionnaire in assessment of 3000 obstetric-gynecologic patients: the PRIME-MD patient health questionnaire obstetrics-gynecology study, *Am. J. Obstet. Gynecol.* 183 (2000) 759–769.
- [26] R.L. Spitzer, et al., Utility of a new procedure for diagnosing mental disorders in primary care: the PRIME-MD 1000 study, *JAMA* 272 (1994) 1749–1756.
- [27] M. Linzer, et al., Gender, quality of life, and mental disorders in primary care: results from the PRIME-MD 1000 study, *Am. J. Med.* 101 (1996) 526–533.
- [28] K. Lesniak-Karpiak, M.M.M. Mazzocco, J.L. Ross, Behavioral assessment of social anxiety in females with Turner or fragile X syndrome, *J. Autism Dev. Disord.* 33 (2003) 55–67.
- [29] N. Molko, et al., Brain anatomy in Turner syndrome: evidence for impaired social and spatial-numerical networks, *Cereb. Cortex* 14 (2004) 840–850.
- [30] R. Adolphs, Trust in the brain, *Nat. Neurosci.* 5 (2002) 192–193.
- [31] L. Sylven, et al., Life with Turner's syndrome — a psychosocial report from 22 middle-aged women, *Acta Endocrinol.* 129 (1993) 188–194.
- [32] E.J. Sutton, et al., Turner syndrome: four challenges across the lifespan, *Am. J. Med. Genet.* 139A (2005) 57–66.
- [33] A.L. Reiss, et al., Neurodevelopmental effects of X monosomy: a volumetric imaging study, *Ann. Neurol.* 38 (1995) 731–738.
- [34] J.L. Ross, et al., Self-concept and behavior in adolescent girls with Turner syndrome: potential estrogen effects, *J. Clin. Endocrinol. Metab.* 81 (1996) 926–931.
- [35] J.L. Ross, et al., The effect of genetic differences and ovarian failure: intact cognitive function in adult women with premature ovarian failure versus Turner syndrome, *J. Clin. Endocrinol. Metab.* 89 (2006) 1817–1822.
- [36] A.K. Watson, J.M. Cheek, Shyness situations: perspectives of a diverse sample of shy females, *Psychol. Rep.* 59 (1986) 1040–1042.
- [37] N.A. Heiser, S.M. Turner, D.C. Beidel, Shyness: relationship to social phobia and other psychiatric disorders, *Behav. Res. Ther.* 41 (2003) 209–221.
- [38] R.P. Mattick, J.C. Clarke, Development and validation of measures of social phobia scrutiny fear and social interaction anxiety, *Behav. Res. Ther.* 36 (1998) 455–470.
- [39] W.E. Hensley, M.K. Roberts, Dimensions of Rosenberg's self-esteem scale, *Psychol. Rep.* 38 (1976) 583–584.
- [40] L.S. Radloff, The CES-D scale: a self-report depression scale for research in the general population, *Appl. Psychol. Meas.* 1 (1977) 385–401.
- [41] K.L.M. Liao, N. Wood, G.S. Conway, Premature menopause and psychological well-being, *J. Psychosom. Obstet. Gynaecol.* 21 (2000) 167–174.
- [42] J.C. Carel, et al., Quality of life determinants in young women with Turner's syndrome after growth hormone treatment: results of the StaTur population-based cohort study, *J. Clin. Endocrinol. Metab.* 90 (2005) 1992–1997.