Neurodevelopmental and Psychiatric Disorders in Females With Turner Syndrome: A Population-based Study

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Research

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Abstract

Background: Turner syndrome is the result of a missing X chromosome, partially or completely, in phenotypic girls. This can cause an array of medical and developmental difficulties. The intelligence quote has previously been described as uneven but considered within normal range. Although a social, intellectual and psychiatric profile is described in females with Turner syndrome, it is unclear to what extent they meet the clinical criteria for neurodevelopmental or psychiatric diagnoses. The aim of this study was to examine the prevalence of neurodevelopmental and psychiatric disorders in females with Turner syndrome.

Methods: A retrospective case-control study was performed with a total of 1392 females with Turner syndrome identified through the Swedish National Patient Register and compared with 1:100 age- and sex matched controls from the general population. The association between Turner syndrome and diagnoses of neurodevelopmental and/or psychiatric disorders were calculated using conditional logistic regression and is presented as estimated risk (Odds ratio, OR, 95% Confidence interval, CI) in females with Turner syndrome compared with matched controls.

Results: Females with Turner syndrome had higher risk of any neurodevelopmental or psychiatric disorder (OR 1.37, 95% CI 1.20-1.57), an eightfold (OR 8.59, 95% CI 6.58-11.20) increased risk of intellectual disability and a fourfold (OR 4.26, 95% CI 2.94-6.18) increased risk of autism spectrum disorder compared with the controls. In addition, females with Turner syndrome had an increased risk of a diagnosis of psychotic disorders (OR 1.98, 95% CI 1.36-2.88), eating disorders (OR 2.03, 95% CI 1.42-2.91) and behavioral disorders (OR 2.01, 95% CI 1.35-2.99).

Conclusions: Females with TS have an increased risk of being diagnosed with any neurodevelopmental and psychiatric disorder. This warrants extensive assessment of intellectual and cognitive functions from early ages and increased psychiatric vigilance should be a part of lifelong healthcare for females with TS.

1. Introduction

Turner syndrome (TS) is a genetic disorder associated with partial or complete monosomy of the X chromosome resulting in karyotype 45,X. TS is one of the most common sex chromosome abnormalities with an incidence ranging from 1/2000-1/2500 in live-born females (1, 2). The complete or partial loss of one X chromosome in girls results in a variation of clinical findings that may include short stature, early loss of ovarian function, cardiac anomalies, hearing loss, visual impairment, and neurocognitive difficulties. The neuroanatomical structure and function of the brain are thought to be highly affected by the characteristics of the X chromosome. The prevailing hypothesis is that the absence or mosaicism of one X chromosome often presents with a specific pattern of cognitive strengths and deficits even if there is a wide spectrum of variation within the group (2–5).

Previous studies on relatively small clinical samples reported that most girls and women with TS have a Full Scale Intelligence Quote (FSIQ) within the normal range but with an uneven intellectual profile with
different domains of relative strengths and deficits (6–13). In addition, females with TS tend to have challenges in specific psychosocial and neurocognitive areas such as learning disabilities and behavioral problems (7, 9, 14). Further, they also have an increased risk of inattention and executive disabilities, as well as impairments in face- and emotion recognition, and direction of gaze and social adaptation (6, 11, 15–21). While some studies show an association between TS and autism spectrum disorders (ASD) (3, 22–25) others found no increased incidence of ASD among individuals with TS (26).

Studies on psychiatric disorders among women with TS are scarce (22–29), but physical stigma, lack of peers, social difficulties, and low self-esteem might contribute to increased levels of depressive and anxiety symptoms thus placing females with TS at risk of developing psychiatric morbidity (9, 30–32).

Given that previous studies are based on small, highly selected clinical samples often without population references, we carried out a nationwide retrospective case-control study to evaluate the risk of clinical diagnoses of psychiatric and neurodevelopmental disorders in individuals with TS in comparison to matched reference individuals from the general population. The secondary aim was to add to the understanding of the X chromosome and etiology of neurodevelopmental and psychiatric disorders by gaining new knowledge of the clinical diagnoses associated with TS.

2. Methods

2:1 National Registers

All citizens in Sweden have a unique personal identification number that is used in all official records and that enables linkage between population-based registers. For research purpose Statistics Sweden has generated a key that converts the personal identification number to a unique ID number that results in pseudonymized, de-identified, data for each individual. The key is not available for researchers (33). We performed a matched cohort study using prospectively collected data from National Patient Register (NPR) and the Total Population Register (TPR) (34). NPR started in 1964 by collecting information on Swedish inpatient care at public hospitals in a few Swedish counties, in 1973 discharge diagnoses for all psychiatric inpatients episodes were added, in 1987 the register had full nationwide coverage of inpatient diagnoses and from 2001 full coverage of all diagnoses from psychiatric outpatient care (35). The Total Population Register (TPR) contains data on life events including birth, death, name change, marital status, family relationships, and migration status updated by the Swedish Tax Agency (34).

2:2 Study design and participants

This study was approved by the Regional Ethical Review Board in Stockholm 2013/862 – 31. Females with TS were identified from NPR, both inpatient and outpatient healthcare, using the following diagnostic codes: ICD-8 759.50, 310.54, 311.54, 312.54, 314.54, 315.54; ICD-9 758G; ICD-10 Q96 (35). Each individual with TS was matched with 100 unaffected females controls by county and date of birth from TPR. As the coverage of the different registries differs between time periods, we stratified the results based on that. In addition, this might also shed light on the possibilities of identifying diagnosis over
time. Given that the NPR has full nationwide coverage of inpatient diagnoses since 1987 and full coverage of all diagnoses from psychiatric outpatient care since 2002, the result was stratified into three different groups depending on year of diagnosis; (1) individuals with TS who were diagnosed before 1987, (2) individuals diagnosed from 1st of January 1987 to 31st of December 2001 and (3) individuals diagnosed from 1st of January 2002 until 31st of December 2013.

### 2:3 Outcomes

The outcomes were diagnosis of neurodevelopmental disorders, psychiatric disorders and suicide attempts. Information of diagnoses of neurodevelopmental and psychiatric disorders was drawn from NPR using the International Classification of Diseases (ICD) codes. Primary outcome measures were: 1) suicide attempts 2) any psychiatric and/or neurodevelopmental disorders, 3) psychotic disorders, 4) mood disorders, 5) anxiety disorders (phobic anxiety disorders; other anxiety disorders; obsessive-compulsive disorders reaction to severe stress, and adjustment disorders; dissociative, conversion, somatoform disorders), 6) eating disorders, 7) psychoactive substance misuse (alcohol and drug misuse), 8) behavioral disorders, 9) ADHD, 10) ASD and 11) intellectual disability (ID). ICD-based definitions are shown in Table 1.
2:4 Statistical Analyses

Similar to previous studies (22, 36–39) we performed a retrospective case-control study to estimate the risk of neurodevelopmental and psychiatric disorders in individuals with TS. Odds ratios (OR) for each neurodevelopmental and psychiatric outcome were estimated from conditional logistic regression models and were stratified on matched sets to account for matching by year and county of birth. The statistical analyses were all conducted with SAS software (version 9.3; Cary, NC, USA).

3. Results

We identified 1392 females registered with TS between 1969 and 2013. In 1969, twelve individuals were registered in NPR with a diagnosis of TS. The oldest individual with TS found in NPR was born 1898 and the diagnosis was registered in 1975.

Analysis of the entire cohort (n = 1392) showed that individuals with TS had an eightfold (OR 8.59, 95% CI 6.58–11.20) increased risk of intellectual disability diagnosis and a fourfold (OR 4.26, 95% CI 2.94–6.18) increased risk of being diagnosed with ASD compared to unaffected controls (Table 2). Individuals with

| Diagnoses                          | 1969-1986 | 1987-1996 | 1997- |
|------------------------------------|----------|----------|------|
| **Suicidal attempts (NPR)/ Completed suicide (CDR)** | E950-E959 | E950-E959 | X60-X84 |
| **Any NDs/ Psychiatric disorders** | 290–315 | 290–319 | F00–F99 |
| **Psychotic disorders**            | 295, 297-299; | 295, 297, 298; | F20-F29 |
| **Mood disorders**                 | 296, 300.40; | 296, 300E, 311 | F30-F39 |
| **Anxiety disorders**              | 300.00-300 30, 300.50-300.99, 307; | 300, 300A-300D, 300F-300X, 308-309 | F40-F45, F48 |
| **Eating disorders**               |           | 307B, 307F; | F50 |
| **Substance misuse**               | 291, 303, 304. | 291, 303, 304, 305A, 305X | F10-F19 |
| **Behavioral disorders**           | -        | -        | F91 |
| **ADHD**                           | -        | 314      | F90 |
| **ASD**                            | -        | 299A     | F84 |
| **Intellectual disability**        | 310-315; | 317-319 | F70-F79 |
| **Personality disorders**          | 301      | 301      | F60-F62, F69 |
TS also had a higher risk of being diagnosed with any psychotic disorders (OR 1.98, 95% CI 1.36–2.88), eating disorders (OR 2.03, 95% CI 1.42–2.91) and behavioral disorders (OR 2.01, 95% CI 1.35–2.99). However, the likelihood of diagnosis of substance misuse (OR 0.64, 95% CI 0.44–0.92) was lower in females with TS compared to unaffected controls. There was no significant association between TS and ADHD, anxiety, death by suicide, suicide attempts, mood disorders, or personality disorders (Table 3).

Table 2. Neurodevelopmental/ psychiatric disorders in girls and women with Turner syndrome compared with age-matched controls (1:100 case/controls).

| Disorder                                      | Turner Syndrome N (%) | Matched Controls N (%) | OR (95% CI)      | P      |
|-----------------------------------------------|-----------------------|------------------------|------------------|--------|
| Any NDDs/psychiatric disorders                | 283 (20.33)           | 21948 (15.77)          | 1.37 (1.20-1.57) | <.0001 |
| Suicide Attempt                               | 19 (1.36)             | 2158 (1.55)            | 0.88 (0.56-1.39) | 0.5682 |
| Psychotic disorders                           | 29 (2.08)             | 1493 (1.07)            | 1.98 (1.36-2.88) | 0.0012 |
| Mood disorders                                | 79 (5.68)             | 8606 (6.18)            | 0.91 (0.72-1.15) | 0.4252 |
| Anxiety, stress-related, somatoform           | 96 (6.90)             | 11210 (8.05)           | 0.84 (0.68-1.04) | 0.1034 |
| Eating disorders                              | 32 (2.30)             | 1609 (1.16)            | 2.03 (1.42-2.91) | 0.0004 |
| Personality disorders                         | 17 (1.22)             | 1720 (1.24)            | 0.99 (0.61-1.60) | 0.9613 |
| Substance misuse                              | 30 (2.16)             | 4635 (3.33)            | 0.64 (0.44-0.92) | 0.0091 |
| ADHD                                          | 22 (1.58)             | 1732 (1.24)            | 1.28 (0.83-1.96) | 0.2771 |
| Other behavioral disorders                    | 26 (1.87)             | 1319 (0.95)            | 2.01 (1.35-2.99) | 0.0017 |
| ASD                                           | 30 (2.16)             | 726 (0.52)             | 4.26 (2.94-6.18) | <.0001 |
| ID                                            | 62 (4.45)             | 760 (0.55)             | 8.59 (6.58-11.20) | <.0001 |
Individuals with TS who were diagnosed before 1987 (n = 328) had an increased risk of receiving a diagnosis of ASD or ID compared to the groups diagnosed in 1987–2002 or later than 2002 until 2013 (Table 3). The risk of any psychiatric or neurodevelopmental disorder is significantly higher in groups that received a diagnosis of TS before 1987 and after 2002 based on current stratification OR 1.59 (1.23–2.04), OR 1.51 (1.21–1.87). In contrast, the group that received a diagnosis from 1987 to 2002 shows a lower (admittedly insignificant) OR 1.12 (0.90–1.41) risk of having any neurodevelopmental or psychiatric disorder. Women who were diagnosed with TS earlier than 1987 compared with controls had a significantly increased risk of having psychotic illness OR 2.61 (1.54–4.42). Those who were diagnosed with TS after 1987 did not show significant increased risks.

### Table 3. Neurodevelopmental/psychiatric disorders in females with TS stratified by year of Turner diagnosis and compared with age-matched controls (1:100 case/controls)

| Diagnosis                      | <1987 | 1987–2002 | > 2001 |
|--------------------------------|-------|-----------|--------|
| Any NDDs/Psychiatric disorders | 41 (1.24) | 554 (17.20) | 1.59 (1.23–2.04) | 0.0006 |
| Social anxiety                 | 8 (1.68) | 981 (2.06) | 0.81 (0.60–1.16) | 0.473  |
| Psychiatric disorders          | 15 (4.57) | 595 (18.1) | 2.91 (1.34–4.42) | 0.0017 |
| Mood disorders                 | 22 (4.62) | 3480 (7.31) | 0.61 (0.40–0.94) | 0.0164 |
| Anxiety stress-related disorders | 28 (5.88) | 4555 (9.57) | 0.59 (0.40–0.96) | 0.0036 |
| Eating disorders               | 19 (3.99) | 793 (1.67) | 2.48 (1.55–3.97) | 0.0008 |
| Personality disorders          | 5 (1.05) | 745 (1.57) | 0.67 (0.41–1.16) | 0.3376 |
| Substance misuse               | 11 (2.17) | 639 (1.04) | 1.49 (0.77–2.92) | 0.2079 |
| ADHD                           | 9 (1.89) | 1983 (4.17) | 0.44 (0.23–0.86) | 0.0096 |
| Other behavioral disorders     | 18 (3.56) | 803 (1.57) | 2.11 (1.15–3.97) | 0.0023 |
| ASD                            | 11 (2.21) | 618 (1.29) | 1.62 (0.90–2.83) | 0.1173 |
| ID                             | 18 (3.65) | 350 (0.66) | 3.65 (2.02–6.52) | 0.0003 |

Individuals with TS who were diagnosed before 1987 (n = 328) had an increased risk of receiving a diagnosis of ASD or ID compared to the groups diagnosed in 1987–2002 or later than 2002 until 2013 (Table 3). The risk of any psychiatric or neurodevelopmental disorder is significantly higher in groups that received a diagnosis of TS before 1987 and after 2002 based on current stratification OR 1.59 (1.23–2.04), OR 1.51 (1.21–1.87). In contrast, the group that received a diagnosis from 1987 to 2002 shows a lower (admittedly insignificant) OR 1.12 (0.90–1.41) risk of having any neurodevelopmental or psychiatric disorder. Women who were diagnosed with TS earlier than 1987 compared with controls had a significantly increased risk of having psychotic illness OR 2.61 (1.54–4.42). Those who were diagnosed with TS after 1987 did not show significant increased risks.

### 4. Discussion

In this population-based study of Turner syndrome we compared the risk of neurodevelopmental and psychiatric diagnoses in girls and women diagnosed with TS with matched reference individuals from the general population. Our study identifies a significantly increased risk of ID and other clinical diagnoses such as psychotic-, eating- and behavioral disorders. The findings also confirm the few previous studies that have shown a high risk of ASD in females with TS (3, 23–25). This is also the first study to report on the risk of psychoactive substance misuse in individuals with TS, showing that girls and women with TS have a lower risk compared to the general population to be diagnosed with drug or alcohol misuse.
The most important finding was the more than eightfold increased risk of ID. The intellectual level in TS is described as slightly lower than average but within normal range (6–8), but with small numbers (n = 50) of TS individuals, previous studies have been largely underpowered to detect any difference in fulfilling the diagnostic criteria for ID. A higher incidence of ASD has previously been shown by Creswell and Skuse (9, 23) however, this is the first study to estimate risk in comparison to unaffected population controls. A contributing factor to identify this high risk of ID and ASD in females with TS in Sweden is probably the national registers covering all individuals, thus including individuals with severe intellectual disabilities or restrictive autistic behaviors that might hinder the ability to participate in studies that require active or challenging participation. Though, the increased incidence of ID and ASD might also reflect the fact that individuals presenting with major intellectual disabilities or restrictive autistic behaviors are more likely to be genetically investigated and thus diagnosed with TS.

The increased risk of ASD in this study is consistent with previous findings of approximately 3% of individuals with TS fulfilling the ICD-10 diagnostic criteria for autism (23) that is twice the estimated incidence for the general population (1.5%) (40). These results reflect previously well-described social difficulties in individuals with TS who in comparison with girls and women in the same age group seem to have fewer friends and engage in fewer social activities (15, 41). The increased interest in social deficits in TS might implicate an increased awareness of ASD or autistic traits associated with TS. Nevertheless, large studies that present incidence, based on diagnostic criteria, are lacking.

Stratifying the results in relation to time of diagnosis provides an interesting opportunity to spot possible differences between the time periods. However, the relatively small sample sizes lead to fewer opportunities to draw reliable conclusions. Individuals with TS who were diagnosed before 1987 (23.6%) had an increased risk of receiving a diagnosis of ASD or ID compared to the groups diagnosed in 1987–2002 or later than 2002. This might, again, reflect that the register only had coverage of discharge diagnoses before 1987, thus including only the women with the most pronounced phenotypes and disabilities in need of inpatient care. In addition, the diagnose and traits of autism has gained more attention during the last decade with changes in the reporting practices and diagnostic criteria, which also might reflect an increase in number of individuals diagnosed with ASD in general (42, 43).

Previous studies have shown a clear association between TS and ADHD (12, 17, 44). Recent studies have shown that the executive dysfunctions common in TS are best described by the diagnostic criteria for ADHD. Surprisingly few individuals in this study had been diagnosed with ADHD. Thus, women with TS may very well be under-diagnosed with ADHD, as these dysfunctions may have been attributed to the diagnosis of TS and not assessed as a separate dysfunction. Our results may primarily reflect a previous lack of knowledge about ADHD and the importance of assessing the diagnosis regardless of being diagnosed with a syndrome.

Regarding the increased risk of psychotic disorders, previous studies have shown that schizophrenia is increased by threefold among females with TS, especially among individuals with 45,X/46,XX mosaic karyotype (45, 46). In comparison, in this study, the odds ratio was slightly lower, 1.98 (95% CI 1.36–2.88),
and included all psychotic disorders, not just schizophrenia. However, evaluating solely the diagnosis of schizophrenia could produce misleading results, especially in children and adolescent, where diagnosis of schizophrenia is rare even if psychotic symptoms has appeared several years earlier (47).

Our results show that girls and women with TS have twice the risk of receiving a diagnosis of eating disorders compared to unaffected controls (OR 2.03, 95% CI 1.42–2.91). There are a few studies on TS and eating disorders, however, in a sample of 46 females with TS, six individuals (13%) were diagnosed with an eating disorders (five with anorexia and one with bulimia) (29). In a European cross-sectional studied with self-reported data of 325 individuals with TS, 10.8% reported eating disorder as a previous or current psychiatric diagnose (3). When stratifying our results, women with a diagnose of TS registered between 1987–2001 had a significantly higher risk of being diagnosed with an eating disorders, which is consistent with the overall prevalence of anorexia nervosa among Swedish female twins 1.20% (48). This might be explained by rates of bulimia increasing during the 1980s and early 1990s, and they have since remained the same or decreased slightly (49). The higher risk of eating disorder in TS may also be a result of ascertainable bias since women with TS have regular medical examinations, thus being diagnosed to a greater extent.

The risk of anxiety or mood disorders in individuals with TS in this study was not significantly increased in comparison to the general population. In contrast, a previous study found that 52% out of 100 females with TS met criteria for a current or a past depressive or anxiety disorders during their lifetime (29). This can suggest that mood and anxiety disorder in TS remains largely undiagnosed. The frequency of mood or anxiety related diagnoses in our study were overall lower in females with TS, with the lowest numbers among women with their diagnose of TS registered between 1987–2001. This could reflect the increased knowledge of the genetic diagnosis of TS at that time and, again, the lack of knowledge to further investigate the psychiatric symptoms, regardless of the diagnosis of TS.

The correct investigation and diagnosis are essential in order to access proper care (32) as well as adjustments in school or at work, training interventions and drug treatment (50, 51). Early detection of sex chromosomal abnormalities and intervention has, in general, been shown to have a positive impact on psychosocial, cognitive, and reproductive ability (32).

Our results support previous molecular findings suggesting an effect of x-linked genetic information in the etiology of neurodevelopmental disorders (52, 53). Further describing the phenotype in TS may also provide better understanding of sexual dimorphism, as well as clues to a deeper understanding of X-linked neurodevelopmental disorders (52, 54)

5. Strengths And Limitation

The strength of this study is the population-based design and prospectively collected data from national registries with nationwide coverage. However, there are limitations related to register-based methodology. The exact karyotype, whether it is mosaicism or not, cannot be distinguished by ICD codes in the registers. We stratified the results to examine whether it would differ between the groups due to tendency
to identify different diagnoses of neurodevelopmental disorders and psychiatric disorders over time. However, no reliable results could be found as the groups became too small and the coverage in the registers varied too much.

Girls and women with TS are under regular care and frequent visits to health care thus increases the risk of ascertainment bias. On the other hand, the results from this study might imply that females with TS are under-diagnosed regarding ADHD. Swedish healthcare is publicly funded with universal access to both primary and non-primary healthcare (55). Most diagnoses in NPR have a positive predictive value (PPV) of 85-95%, but the figures vary according to diagnosis (35). Among psychiatric diagnoses, PPV have ranged from 86 to 95% for schizophrenia (56, 57), and 96% for ASD (58). However, the results only reflect diagnoses, and as always in registry studies, the diagnosis cannot be verified by going back to the patient's chart.

**Conclusions**

This study confirms prior findings regarding the phenotype of TS but also adds new knowledge by presenting higher prevalence of ID and ASD than previously reported. These findings indicate that assessments related to development, intellectual functions and psychiatric symptoms are warranted from an early age in females with TS in order to offer proper treatment, training interventions and adjustments in their everyday life. Although we argue that TS, based on its genetic constitution, may be predisposed to conditions that are connected to brain development, it is essential to remember that association should not be considered equal to causation.

**Abbreviations**

ICD, International Classification of Diseases,

NPR, National Patient Register

TPR, Total Population Register

CDR, Cause of Death Register

NND, Neurodevelopmental disorders

ADHD, Attention-deficit, hyperactivity disorder

ASD, Autism spectrum disorders

**Declarations**
Ethics approval and consent to participate

1.1 Ethics approval: This study was approved by the Regional Ethical Review Board in Stockholm 2013/862-31.

1.2 Consent to participate: Not applicable.

Consent for publication

Not applicable.

Availability of supporting data

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

ANo, And, CA and LF developed the idea and topic of the manuscript and drafted the method. AB did the statistical analyses. HAB, AB and HE each wrote and edited the manuscript. All authors contributed to the ideas expressed in the manuscript. All authors read and approved the final manuscript.

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