Socioeconomic parameters and mortality in Turner syndrome

Kirstine Stochholm, Britta Hjerrild, Kristian Havmand Mortensen, Svend Juul, Morten Frydenberg and Claus Højbjerg Gravholt

Department of Internal Medicine and Endocrinology, Aarhus University Hospital, Norrebrogade 44, DK-8000 Aarhus C, Denmark, Departments of 1Epidemiology and 2Biostatistics, School of Public Health, Aarhus University, Aarhus, Denmark

(Correspondence should be addressed to C H Gravholt; Email: ch.gravholt@dadlnet.dk)

Abstract

Background: Turner syndrome (TS) is characterized by hypogonadism, short adult height, increased morbidity and mortality, contrasted by self-reported normal quality of life and perception of health. Small studies have indicated a similar level of education compared with the background population.

Aim: To study the socioeconomic profile in TS and the impact of these factors on mortality.

Materials and methods: Register study using Danish nationwide registries. Nine hundred and seventy-nine TS females and 94,850 controls were included. Information concerning cohabitation, motherhoods, level of education (bachelor degree), income, retirement, and death were obtained.

One hundred and three TS and 5,989 controls died during the study period. For the socioeconomic parameters, median age at first relevant episode was calculated. Income was analyzed using conditional logistic regression and the other parameters using Cox regression.

Results: In comparison with controls, TS had significantly fewer partnerships (hazard ratio (HR): 0.45), fewer motherhoods (HR: 0.18), and retired earlier (HR: 1.8). After the diagnosis of TS, the risk of retiring was increased. Educational attainment (HR: 1.0) as well as risk of unemployment was similar. Before the age of 30, low income was significantly more frequent; hereafter, it was similar to controls. Mortality was significantly increased (HR: 2.9) and slightly lower after adjustment for cohabitation and education (HR: 2.7).

Conclusions: A divergent socioeconomic profile is apparent, with a reduced proportion of TS persons finding a partner and becoming mothers. The educational level was similar to controls. The increased mortality in TS was not materially affected after adjustment for cohabitation and education.

Introduction

Turner syndrome (TS) is characterized by short stature, ovarian dysgenesis, and infertility. The chromosomal background is 45,X, a structurally abnormal X chromosome (such as isochromosomes or ring chromosomes), a mosaic condition (i.e., 45,X/46,XX), or karyotypes with Y chromosome material (1). The life of a girl and woman with the syndrome is affected by the negative impact of a broad range of syndrome-associated features and subsequently by a substantially increased morbidity (2) and mortality (3, 4, 5).

Some aspects of socioeconomic outcome in TS have been studied by use of questionnaires. Differences in objective and perceived health, psychosocial status, and quality of life have been investigated (6, 7, 8, 9, 10), and the findings are unequivocal with an overall rather normal self-rated quality of life, despite a significantly increased burden of health problems. However, all these smaller studies could be subject to ascertainment bias and thus the conclusions reached from these studies could lack external validity. In another sex chromosome abnormality, Klinefelter syndrome (47,XXY), we recently documented severely inferior socioeconomic conditions with important influences on mortality in a similar setup with ascertainment of all diagnosed patients nationwide (11). We therefore hypothesized that a similar poor socioeconomic pattern would be present when studying all diagnosed females with TS in a nationwide setup.

Information regarding retirement is limited in TS, and differences in socioeconomic parameters before and after the diagnosis have not been investigated. Furthermore, the effect of a possibly altered socioeconomic status on mortality is not known. Thus, in order to avoid the possible selection bias in questionnaire studies, and to shed further light on the seemingly paradoxical findings in questionnaire studies, we i) identified the entire cohort of diagnosed TS persons in Denmark in a national registry, ii) analyzed the socioeconomic parameters such as cohabitation, education, income, motherhood, and retirement before and after the Turner diagnosis compared with an age-matched female background population, and iii) analyzed mortality with and without adjustment for cohabitation and education.
Materials and methods

Study population

Using the Danish Cytogenetic Central Registry, we identified all females diagnosed with a karyotype compatible with TS in Denmark by January 2009. This registry contains all information regarding cytogenetic analyses undertaken nationwide since 1960. For every TS person, Statistics Denmark identified up to 100 age- and calendar–time-matched controls (born same month and year) from the female background population. The controls were alive and living in Denmark on the date their index person was diagnosed. As all Danish citizens from 2nd of April 1968 were given a unique identification number (Central Person Registrations (CPR)-number) from the Central Office of Civil Registration, it is possible from the various registries to identify all persons registered and to ensure a one-to-one coding within and between the registries. Foreigners are given a CPR number including their initials and are clearly different from Danish CPR numbers. Statistics Denmark registers all relevant information regarding change of address, start and end of an education, income, childbirths, retirement, etc. enabling us to collect these data and link them with information regarding mortality.

Socioeconomic outcome parameters

From Statistics Denmark, we retrieved information regarding the following events: cohabitation with a partner, achievement of an education, childbirth, retirement, emigration, and death. Income was registered annually.

Cohabitation with partner

We retrieved all persons’ civil status on 1st of January each year during the study period. Data were available from 1980 through 2007. The event was first change from being single to be cohabitating with a partner. We only used information on persons without any previous registration of a partner and who were between 18 and 70 years old.

Education

Data were category of education and dates for achieved education. Educational categories registered were primary school, high school, vocational training, and a bachelor degree (e.g. laboratory technician or nurse). An achieved bachelor degree was considered ‘an education’. The event was first achieved bachelor degree in a person between 18 and 40 years. The retrieved data included all education achieved from August 1961 to May 2008.

Income

Information on annual income, i.e. the taxable income before deductions, was given from 1980 to 2006. Only persons between 18 and 70 years of age with an income registered were included. For each calendar year, each TS person was classified as having a higher or a lower income than the median compared with the controls. Because retired persons are typically on a fixed and reduced income, all retired persons were excluded from the analysis from the year of retirement and onward.

Childbirths

We retrieved the mothers’ age in years when giving birth. All analyses were performed in firstborn children only, and we included only women between 15 and 50 years of age. All children born or adopted were registered from 1942 until 2007 with a linkage to both of their parents.

Unemployment

Data were only reported on unemployed persons and given annually as number of days with unemployment. We considered no registration as well as unemployment of <1% as being fully employed, the remaining were considered unemployed the relevant year. Only persons between 18 and 59 years of age with an income registered were included. As retired persons are not at risk for unemployment, they were censored from the analyses from the year of first registration of retirement and onward. Information was available annually from 1985 to 2007.

Retirement

We defined retirement as due to age, sickness, and voluntary choice. A person was considered retired the first year money was received due to retirement and onward, regardless of a later return to the labor market. Data were given annually and available from 1984 to 2006. All calculations were performed on persons between 18 and 70 years of age.

Mortality

The International Classification of Diseases (ICD) 8th edition was used until 1993 and ICD-10 from 1993 and onward. For all analyses, we only used the primary cause of death. We translated all diagnoses from ICD-8 to ICD-10 and categorized the deaths into the 19 chapters corresponding to ICD-10 for analyses of cause-specific mortality. Hazard ratios (HRs) adjusted for age and calendar time were calculated for all chapters, as well as for all-cause mortality. Further, we adjusted for cohabiting status and education. The dates of death were updated through December 2008, and specific causes of death were updated through December 2006.

Approval

This study was approved by the Danish Data Protection Agency. According to the Danish Act on Processing of Personal Data, a registry study without contact to
the persons involved does not need verbal or written consent.

**Statistical analysis**

For the socioeconomic parameters, median age at first relevant event was calculated. Kaplan–Meier estimates were constructed for the first experience of cohabitation, first child, and first retirement. The overall time at risk started at the relevant entry age (e.g. 15 years) and ended at the date of first event or at the relevant exit age (e.g. 50 years), whichever came first. Time at risk before diagnosis ended no later than the date of diagnosis, and time at risk after diagnosis started no earlier than the date of diagnosis.

HR and P values were calculated using Cox regression where each TS person and her matched controls were a stratum, hereby adjusting for age and calendar time. Finally, we analyzed mortality adjusted for cohabitation and educational status.

Income was analyzed annually using conditional logistic regression, where each case and her matched controls were one stratum.

Using the median year at diagnosis (1986), we divided the TS persons into two cohorts, one for those diagnosed early (before the median year of diagnosis) and one for those diagnosed late (after the median year of diagnosis). For childbirths, the fertility rate was calculated as annual number of children born to TS persons or controls divided by number of persons aged 15–49 years the relevant year. Changes in fertility rate from 1980 were analyzed using Poisson regression.

The average fertility rate was calculated as the average number of childbirths divided by the average number of women aged 15–49 years during the study period. We also divided the year of birth in 5-year intervals and examined trends in mortality over time.

All results are shown with 95% confidence intervals (CIs), or with range if relevant, and P < 0.05 was considered statistically significant. We used Stata 11.0 (Stata Corp., College Station, TX, USA) for all calculations.

**Results**

In Danish Cytogenetic Central Registry, 979 persons with TS were identified, and Statistics Denmark identified 94 850 controls. Those TS persons who had no registrations due to age < 15 years during the entire study period were excluded from the following calculations, as well as their controls. No controls were retrieved for one TS person for unknown reasons; she was excluded from all analyses. Thus, data were available for 831 TS persons and their 80 975 controls. The TS population was divided into 45,X (n = 319),
mosaic (45,X/46,XX) (n=167), and other karyotypes (n=345). Table 1 shows the socioeconomic parameters of the subgroups.

**Cohabitation**

Before the diagnosis the HR of initiating cohabitation with a partner for the first time was 0.82 (95% CI: 0.69 to 0.99), and after the diagnosis the HR was 0.34 (95% CI: 0.30 to 0.40). Figure 1 outlines the proportion of persons who ever have had a partner (HR 0.45, 95% CI: 0.40 to 0.50, P<0.001), showing a significantly decreased number of TS with a partner. At the age of 30 years, 60.2% of all TS persons and 88.5% of all controls at risk at least once had a partner.

**Education**

The HR of TS achieving a bachelor degree was 1.00 (95% CI: 0.87 to 1.15), without any discrepancy before and after the diagnosis. At the age of 30 years, 64.8% of all TS persons and 66.3% of all controls at risk had achieved a bachelor degree.

**Income**

The proportion of TS persons with an income below the median was increased before the age of 30 years, and hereafter similar to controls (Fig. 2).

**Motherhood**

The proportion of women who had given birth was lower in the three karyotype groups compared with controls (Fig. 3). Focusing on the annual number of children born between 1969 and 2007 per women between 15 and 50 years of age, we identified a significantly increasing fertility in TS persons (P<0.005) and a significantly decreasing fertility in controls (P<0.001) (no data shown). The average fertility rate was 20.1 (95% CI: 17.9 to 22.6) and 63.7 (95% CI: 63.3 to 64.2) children per 1000 women respectively. The HR of having a child before the diagnosis was 0.29 (95% CI: 0.24 to 0.35) and after the diagnosis 0.13 (95% CI: 0.11 to 0.16). The HR of adoption among TS was 0.42 (95% CI: 0.19 to 0.94) (six TS had adopted seven children; 631 controls had adopted 707 children); TS were significantly older at first adoption (30.5 vs 23.0 years, P<0.05).

**Unemployment**

Unemployment was virtually unaffected by age (Table 1 and Fig. 4) and basically similar to controls.

**Retirement**

The HR of retiring before the diagnosis was 0.69 (95% CI: 0.34 to 1.39), and after the diagnosis, it was 2.0 (95% CI: 1.7 to 2.4) (Fig. 5). By the age of 30 years, 1.9% of the background population and 7.0% of the TS persons were retired.

**Mortality**

The HR for all-cause mortality, only adjusted for age and calendar time, was 2.9 (95% CI: 2.4 to 3.5), with no change in mortality over time. All chapters had an increased though not necessarily significant HR. Adjusted for cohabitation and education, the all-cause HR was slightly reduced to 2.7 (95% CI: 2.2 to 3.3). The all-cause excess mortality, i.e. the difference between the observed and the expected mortality, in TS persons with
known causes of death, was 52 persons, whereof 21 (40.4%) died due to cardiovascular diseases. There was no pattern in the remaining excess mortality (no data shown).

**Effect of age**

Dividing the cohort into two, diagnosed before or after 1986, we found a significantly worse outcome for those diagnosed before 1986: cohabitation (HR before 1986 vs HR after 1986: 0.31 (95% CI: 0.27 to 0.37) vs 0.66 (95% CI: 0.57 to 0.77)); a bachelor degree (0.87 (95% CI: 0.71 to 1.06) vs 1.05 (95% CI: 0.85 to 1.29)); motherhood (0.09 (95% CI: 0.07 to 0.12) vs 0.35 (95% CI: 0.29 to 0.42); and retirement (2.44 (95% CI: 2.01 to 2.96) vs 1.17 (95% CI: 0.77 to 1.76)). It is important to note that the proportion of females with 45,X makes up a larger part of the females diagnosed before 1986 (53%) than after 1986 (23%), and this may of course affect the results.

**Discussion**

In this nationwide study including all diagnosed Danish persons with TS, we have identified a social profile different from an age- and calendar time-matched female background population. These novel data show a strong association between TS, labor market marginalization, economic disadvantage, and singleness in these persons. Further, although the number of children born to Turner women was significantly reduced, it is noteworthy that focusing on the mosaic subgroup, data were encouraging indeed with almost half of the women at risk becoming mothers. We identified a rather profound consequence of being diagnosed with TS on the chances of finding a partner and on retiring. On the other hand, after the third decade TS persons had a median income similar to controls, and the rate of unemployment was similar to controls at all ages. When adjusting for cohabiting status and education, the significantly increased mortality changed only marginally. Thus, in persons with TS, socioeconomic parameters are affected in a variable fashion, some parameters in a positive direction and some in a negative way.

We focused on TS persons before and after the diagnosis as these cohorts are not necessarily alike. The association between being diagnosed and initiating cohabiting, becoming a mother, and retiring was high. These associations have not been described before. The reduced chance of finding a partner indicates that the awareness of the TS diagnosis to some degree may influence the TS persons’ expectations or self-esteem. It also indicates that the phenotype of the TS persons diagnosed late is not as affected as those diagnosed early, as shown previously in a Swedish cohort (12). Nevertheless, we assume that a puberty as similar to peers as possible in onset and timing is important for the individual TS person, in line with previous findings of an increased quality of life in those with spontaneous pubertal timing (13).

We consider the difference in retirement before and after the diagnosis to be due to easier acceptance of an application for retirement when a syndrome is diagnosed. From our data, it is not possible to identify whether the diagnosis occurred as a consequence of a change in health or social circumstances or the information about the diagnosis had social consequences. This finding does not indicate that a late diagnosis in TS persons *per se* is better for the individual.
person. A late diagnosis rather may indicate a less affected phenotype with a socioeconomic position more similar to the background population. A limitation is the lack of clinical information on the study population, rendering it impossible to correlate any of our findings with clinical information, for instance the frequent otological problems (14), or treatment with sex steroids, which not all eligible TS persons are prescribed (15, 16).

Previous questionnaire studies identified a similar level of educational attainment in adult TS persons and controls (9, 17), or an increased level in adult TS persons diagnosed as children (10), which is in line with our findings. We have no obvious explanation for the decreased median income in the younger years, and excluding all persons who retired before the age of 50 years from the entire analysis only changed the findings marginally. It is also interesting that the rate of unemployment was similar to that of controls, and this serves to underline that, if capable of working, most females with TS do well in the workplace. We consider the different findings between TS persons diagnosed before and after 1986 to be due to a more severe impact of the syndrome in former times. An effect both due to a changing composition of karyotypes in cohorts of TS females diagnosed in different decades (i.e. more females with 45,X in older cohorts), and probably better medical care and increased awareness and information about TS. We therefore suggest that future socioeconomic analyses in TS cohorts take karyotype and time period of diagnosis into consideration.

Infertility is of major concern in TS persons (15). Italian data in 522 TS persons described 84 women with spontaneous pubertal development, whereas 30 women had regular menstrual cycles more than 9 years after menarche; among these 84 women, only three (3.6%) pregnancies were reported (18). However, spontaneous pregnancies are reported, also in 45,X persons (19, 20). With the limited data available on births in TS persons and the well-known hypogonadal problems (21), the finding of 77 (46.1%) mothers in the 45,X/46,XX subgroup is striking but is backed up by recent Swedish data (21). We have no data to determine whether the Danish TS persons were the biological mothers, but many may have conceived after egg donation, which is becoming increasingly common among TS (22, 23). Generally, the different outcomes in the three subgroups, with the mosaic subgroup being least affected, is important to note.

That mortality is linked to social factors is not surprising (24). However, with the data presented, we show that a negative socioeconomic profile only has a minor effect on the increased mortality in TS persons. Our finding of the significantly increased HR of 2.9 (95% CI: 2.4 to 3.5) is similar to our previous finding of a standardized mortality ratio of 2.86 (95% CI: 2.18 to 3.55) in a subgroup of the subjects presented here (n = 781) (4) and to the finding in British women with TS (n = 3439) where a standardized mortality ratio of 3.0 (95% CI: 2.7 to 3.4) was identified (3). The excess mortality was primarily due to deaths from cardiovascular disease, as also shown previously (3, 4), and was unchanged after adjustment for cohabitation and education. Further data are needed in order to fully explain the excess mortality in TS persons.

Conclusion

In summary, we present a divergent socioeconomic profile of females with TS, with a negative association between being diagnosed with TS and the chances of finding a first partner, a positive association between the chances of retiring, while educational level was similar to controls. Income was significantly decreased in TS persons until the age of 30 years. The number of mothers in the TS cohort was significantly decreased, however, with a surprisingly high number of mothers. All-cause and cardiovascular mortality compared with an age-matched female background population was significantly increased, and this remained increased when adjusting for social parameters. Further studies are needed to determine whether the socioeconomic profile is amenable to improved medical treatment.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

K Stochholm was supported by a research grant from Central Denmark Region and from Danish Ministry of Science, Technology and Innovation.
Author contribution statement

K Stochholm and C H Gravholt made substantial contributions to conception and design, as well as analysis and interpretation of data and drafted the manuscript. S Juul, B Hjerrild, K H Mortensen, and M Frydenberg made contributions to conception and design, interpretation of data, and revised it critically. C H Gravholt made substantial contributions to conception and design and interpretation of data and revised it critically. All authors have given final approval of the version to be published. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgements

Statistics Denmark supplied the data regarding controls.

References


