

The epidemiology of Turner syndrome

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Abstract. The epidemiology of Turner syndrome is largely unknown. A few studies of prevalence and incidence of the syndrome have been performed based on large chromosome surveys, and based on these studies it may be estimated that Turner syndrome occur in 50 per 100,000 liveborn females. A considerable delay in diagnosis of new cases of Turner syndrome exists in all studied populations, emphasizing clinical vigilance, and some are only diagnosed upon reaching adulthood. Based on available data morbidity is increased due to a number of conditions and diseases. As a result mortality is also increased. Better care and medical treatment of females with Turner syndrome will likely reduce the increased morbidity and mortality. © 2006 Elsevier B.V. All rights reserved.

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1. Introduction

The study of Turner syndrome (TS) has largely been based on smaller clinical studies and many case reports, since the initial descriptions by Turner and Ullrich [1,2]. Knowledge concerning any condition based on such data may introduce ascertainment bias, as seen in hospital based studies with patients skewed towards a more severe phenotype, patients ascertained according to medical specialty, or the specific interest of the researcher. Population-based epidemiology can offer a broader and hopefully a more unbiased view of a condition, with the potential of generating new hypotheses, which can then be examined in more detail in clinical studies.

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Early epidemiological studies in the seventies and eighties focused on the prevalence of TS, and were, by design, retrospective or prospective chromosome surveys of consecutive newborns at different institutions in Europe, USA and Japan [3–7].

2. Incidence and prevalence

2.1. Prenatal studies

The prenatal prevalence is much higher than the postnatal prevalence [8]. This indicates that a high rate of conception of TS fetuses occurs. This is illustrated by a very high prevalence of Turner syndrome karyotypes after chorion villus sampling (week 11) of 392 TS fetuses per 100,000 female fetuses compared with a prevalence after amniocentesis (week 16) of 176 per 100,000 [8]. There is a well-described increased intrauterine mortality, especially during the first trimester (peaking in gestational week 13) [9], but after this period there is no or only slightly increased intrauterine mortality [8]. Prenatal diagnosis of TS is not always correct, especially when taking into account mosaic cases [8,10–13], and it is even more complicated in rare cases with twins [14]. Prenatally ascertained mosaic cases have a more benign course than postnatal ascertained cases, which might be due to postnatal ascertainment bias, with the less severely affected cases not being identified postnatally.

2.2. Postnatal studies

The prevalence of TS is based on a number of cytogenetic studies with estimates ranging from 25–210 per 100,000 females [3–7,9]. We pooled data from a number of cytogenetic studies performed more than twenty years ago and based on these studies we estimated a true prevalence at birth of 50 TS per 100,000 females [8], making it one of the more common chromosomal disorders. Currently, the diagnosis of TS is made more infrequent than would be expected from the original cytogenetic surveys [8,15,16], and a considerable delay in diagnosing girls and adolescents with the syndrome is obvious [15,16]. In Denmark the number of TS born during 1970–93 and diagnosed no later than 1996 was 32 per 100,000 liveborn girls [8], leaving some hypothetical 18 TS per 100,000 liveborn TS undiagnosed. Updated Danish data on prevalence shows that more TS are diagnosed with time. When re-assessing prevalence in 2006 the prevalence of TS born during 1970–93 had risen to 40 per 100,000 liveborn girls [17].

In a recent Danish study, the average age at diagnosis of TS was 13, 14 and 19 years for females with the classical karyotype 45,X, isochromosome Xq, or any other karyotype associated with Turner syndrome (Stochholm et al., unpublished results). The delay is remarkable and surprisingly similar among females with the 45,X and an isochromosome Xq of 13 and 14 years, while individuals with other karyotypes like 45,X/46,XX, deletions of either Xq or Xp, and karyotypes involving a Y-chromosome had an even longer median delay of 19 years. Previously, in a *pediatric population* it was shown that the delay to diagnosis was on average 7.7 years [15]. Likewise, in a Belgian *pediatric population* it was found that the median age of diagnosis was 6.6 years, and improving in comparison with an earlier census 12 years earlier [16]. TS with

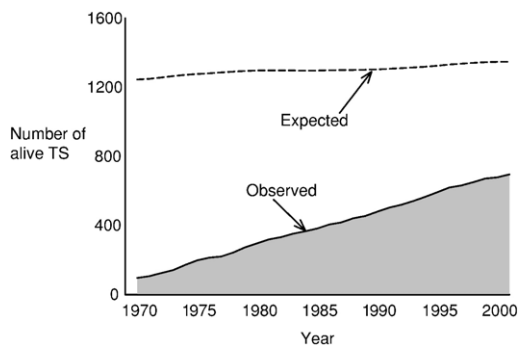


Fig. 1. The absolute number of females with Turner syndrome diagnosed in Denmark during the period 1970–2001 and illustrated by the solid line. Individuals dying or emigrating are subtracted. The dashed line indicates the expected number of Turner syndrome, assuming a true prevalence of 50 TS per 100,000 at birth, and similar mortality as in the general population. Analysis based on all postnatally diagnosed females with Turner syndrome.

karyotypes other than 45,X present longer delays due to the fewer stigmata they typically exhibit, although final height is reduced to the same degree as in females with 45,X [18–20]. Most of these females will also display ovarian failure or very premature ovarian failure [21], and the delay in diagnosis is therefore quite striking. In addition, we estimate that only one-tenth of females with TS were diagnosed in 1970, a fraction that had increased to about one-half by 2001 (Fig. 1).

Thus, the delay in diagnosis cannot simply be explained by lack of manifestations of TS in different populations. In addition to delay in diagnosis of the syndrome during childhood and adolescence, it must be emphasized that TS is also frequently diagnosed in adults (Fig. 2).

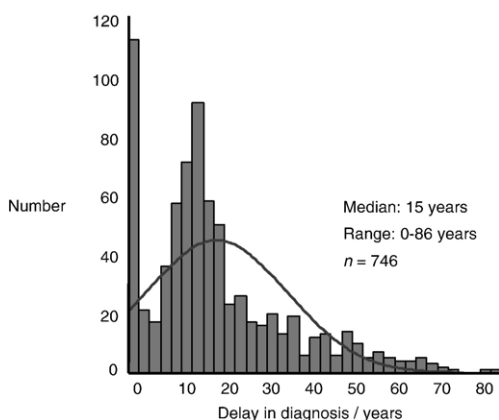


Fig. 2. Delay in Turner syndrome diagnosis from birth. The X-axis indicates the chronologic age at diagnosis of Turner syndrome, with each bar illustrating a 2.5-year period. Data are from the Danish Cytogenetic Central Register from 1910 to 2000 and include all females with a karyotype that can be associated with TS.

Table 1
The distribution of different diagnoses on karyotype groups

	45,X (%)	All other karyotypes (%)	<i>P</i> ^a
Cancers	42	58	0.7
Endocrine diseases	30	70	0.005
Anemia and other diseases of the blood	43	57	0.8
Cardiovascular diseases	30	70	0.03
Diseases of the liver, gall bladder and pancreas	36	64	0.4
Locomotor diseases	38	62	0.5
Congenital malformations	67	33	0.006
Fractures	49	51	1.0

Females with TS were divided into TS with 45,X or all other karyotypes. Diagnoses are grouped into chapters, and only selected diagnose chapters are shown. Data are based on 595 females with TS studied during 1984–1993.

^a Comparison of one diagnosis with all other diagnoses. Pearson's χ^2 test.

2.3. Morbidity and mortality

Morbidity is clearly increased in Turner syndrome. In a study of all diagnosed females with Turner syndrome ($n=594$; years at risk=5410 years) and the background population of women ($n=2,594,036$) in Denmark, we compared incidence rates of diseases suspected to occur with increased frequency [22]. The relative risk (RR) of an endocrine diagnosis in Turner syndrome patients is 4.9 (95% confidence interval (CI)=3.6–6.4), being accounted for by an increased risk of hypothyreosis, thyroiditis, type 1 and 2 diabetes. Likewise, the risk of ischemic heart disease and arteriosclerosis, hypertension, and vascular disease of the brain, was increased. The risk of other conditions like cirrhosis of the liver, osteoporosis, and fractures was also increased, as were the risks for congenital malformations of the heart, of the urinary system, of the face, ears, and neck. The relative risk for all cancers was 1.35 (95% CI=0.70–2.35), with only the risk of colonic and rectal cancers being significantly elevated (RR=4.94). Congenital malformations were most frequent among women with the 45,X karyotype, while endocrine diseases, heart disease, hypertension, and

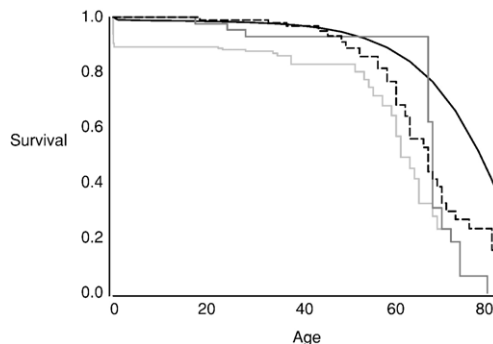


Fig. 3. Kaplan–Meier plots of cumulated mortality in the general population (black line), females with 45,X (light grey line), females with an isochromosome Xq (dark grey line), and females with all other karyotypes associated with TS (dashed black line). A total of 741 postnatal cases were identified fulfilling the criterion to contribute time at risk during 1970–1999.

arteriosclerosis were more frequent in women with other Turner karyotypes (Table 1) [22]. A study using a different registry, the Cancer Registry, found similar results concerning risk of cancer [23]. Only the risk of cancer of the colon was uniformly found to be increased, possibly due to estrogen deficiency.

Mortality is also increased in Turner syndrome. In a British cohort study ($n=400$, years at risk=8609, deaths=62) the relative risk of death was 4.2 (3.2–5.4) [24], with increases due to diseases in the nervous, digestive, cardiovascular, respiratory and genitourinary systems. Death due to cancer was lower than expected, corroborating the Danish morbidity studies [22,23]. Earlier, Price et al. also found mortality to be increased three-fold, especially in females with congenital malformations [25]. Furthermore, they found aortic dissection to be the cause of death in 3 cases, which was greatly in excess of the expected. Omitting patients with congenital malformations from the statistical analysis reduced the mortality ratios to normal levels.

Recently, we have found an overall increased mortality with a standardized mortality ratio (SMR) of 2.86 (Fig. 3) (Stochholm et al., unpublished results). The cause-specific mortality was increased for coronary diseases, congenital malformations, endocrine, nutritional and metabolic diseases, as well as “other causes”. However, we could not find an increased risk of dying from pneumonia, or other diseases of the respiratory system, or of diseases of the digestive and genito-urinary systems, as found previously by Swerdlow et al. [24]. Interestingly, we observed an almost significant decrease in total mortality over the three decades of study. From studying individual death certificates it could be seen that diabetes indeed was a frequent contributing cause of death, even in cases where it was not the underlying cause of death. We found a considerably increased risk of congenital anomalies as a cause of death, and although we cannot derive such information from our data, it is likely attributable to malformations of the heart and great arterial vessels. We recently studied all observed TS cases with aortic dissection in Denmark, including both deceased (included here) and surviving individuals with TS, and estimated that 1.4 in 100 females with TS would suffer from aortic dissection and at a strikingly young age [26]. The increased risk of coronary disease may well be explained by the very frequent occurrence of hypertension (~50%) [22,27–29], increased carotid intimal thickness, aortic augmentation index and pulse-wave velocity [30,31], and lipid abnormalities found by some [32], but not all investigators [33].

Thus, mortality in TS is increased due to several reasons, which are potentially amenable to proper treatment. We know that most females with TS in Denmark receive HRT (more than 80%) [34], while fewer American TS report the use of HRT (70%) [35]. While HRT recently has been nearly abandoned in the post-menopausal setting, there are no data from randomized studies on the impact of HRT on mortality in premenopausal women deprived of endogenous estradiol production. Epidemiological data from female patients in the pre-menopausal age-group with hypopituitarism suggest that treatment with HRT improves survival [36].

3. Conclusion

Data on prevalence and incidence of TS is based on old cytogenetic surveys. There is a considerable delay in the diagnosis “Turner syndrome” in many cases, and some are not diagnosed before adulthood. Morbidity and mortality is increased, but the aetiology of the

abnormalities that leads to this rather substantial increase is not clear. Proper HRT may curb the increased morbidity and mortality, however there is an urgent need for proper studies documenting an effect of HRT in a premature ovarian failure setting.

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