



Preface

The multidisciplinary conference “Wellness for Girls and Women with Turner Syndrome” was held in April 2006 in Washington DC. The famed cherry blossoms had unfortunately vanished in a storm, but nevertheless the conference was conducted in high spirits, and a broad range of new and important data was presented and discussed. In particular, the rapid advances in genetic screening, cardiovascular imaging and assisted reproductive technology in recent years presented novel opportunities and challenges for the caregivers of girls and women with Turner syndrome (TS).

Prenatal cytogenetic screening is now very widespread, partly because many women are having pregnancies in mid-30’s and beyond, and are concerned about the risk of Down syndrome or other trisomies. Sex chromosome anomalies are detected more commonly than any of the trisomies and thus many fetuses are incidentally diagnosed with TS between the 3rd and 4th month of pregnancy. Retrospective analyses suggest that girls with incidental, prenatal diagnoses may have a relatively mild phenotype compared with girls diagnosed based on clinical features in the years after birth. Very little prospective data on the outcome of such incidental prenatal TS diagnoses is available, because many such pregnancies are terminated. Given the advances in diagnosis and care for girls and women TS and the good quality of life reported in recent surveys, the high rate of elective termination of TS ‘incidental catch’ suggests that prospective parents and their counselors may not have accurate, up-to-date information. Hence, there was extensive discussion on how to disseminate more current information throughout the genetic counseling and obstetrical communities, and among TS support group.

The recent development of relatively inexpensive PCR-based methods for detecting X-chromosome aneuploidy on microscopic amounts of blood is likely to find application in newborn screening before too long. There were discussions on the advantages of identifying the many girls that usually go undiagnosed, a percentage that is 35% or even higher. For example cardiac screening may detect subtle anomalies in TS such as bicuspid aortic valve that are clinically silent yet require treatment with antibiotic prophylaxis, and so on. In addition, early detection could allow early treatment to prevent short stature and early intervention in identifying and treating learning problems, potentially sparing the parents from years of searching for explanation of their daughter’s ‘special qualities’.

Another possible advantage of early diagnosis is the ability to ‘rescue’ oocytes or ovarian tissue before the process of early attrition produces complete and irreversible reproductive failure. On the other hand, such widespread postnatal screening is likely to identify many individuals that might never have been identified on clinical grounds, giving rise to new problems. It was agreed that when molecular screening of newborns for TS is offered, positive findings will need karyotype confirmation, an infrastructure for follow-up and treatment of the patients with sex chromosome abnormalities, and support services to help parents and caregivers deal with the uncertainties inherent in this type of diagnosis.

The use of sensitive genetic screening to search for ‘cryptic’ Y-chromosome material in girls with TS was somewhat controversial. The rationale for screening for Y-material is of course to identify patients at risk for gonadoblastoma. There was general agreement on the need for PCR-based or FISH testing for Y-chromosome material in girls that are virilized or have karyotypes with marker chromosomes. However the consensus was that searching for Y-material in normal 45,X TS patients is not indicated, because the risk for false positives leading to unnecessary gonadectomy and psychic trauma is likely higher than the risk of cryptic Y-material being present and then leading to a clinically significant tumor in totally asymptomatic monosomic girls.

In connection with this topic, the group recognized that we do not know the actual risk for a clinically significant gonadal tumor in TS patients with Y-material. The recommendation that all patients with Y-material have a prophylactic gonadectomy is based on case studies noting development of invasive or metastatic tumors in a heterogeneous population of individuals with variable degrees of “gonadal dysgenesis”, most virilized to some extent. This guideline has been widely followed, and the examination of the gonadal material retrieved from TS patients reveals benign, microscopic gonadoblastoma in about 12%. It is completely unknown what percent of these benign cells would eventually transform to a clinically significant, invasive tumor. The issue is non-trivial, because of concern for potential loss of fertility, since women with Y-chromosome in the circulation may have functional ovaries and because one has concern about physical and psychological trauma associated with this invasive procedure in young girls. Given the small numbers of TS patients with Y-chromosome material, a well-designed clinical trial to compare efficacy of gonadectomy vs. ‘watchful waiting’ is not a realistic prospect, however registry data from England and Denmark did not report any deaths from gonadal tumors. Given the lack of evidence for an *alternative* approach to this situation, the consensus supported prophylactic gonadectomy, but only after full and open discussion with the family and/or patient of the limited knowledge of outcomes in this matter, and the provision for psychological support and preservation of any available ovarian follicles.

Some major changes in recommendations for cardiovascular monitoring in girls and women with TS issued from this 2006 conference. Magnetic resonance imaging/angiography has revolutionized our view of cardiovascular involvement in TS. This imaging is not hindered by obesity, unusual chest anatomy or bony structures and can visualize the aortic valve, entire aortic arch as well as other major vessels in the neck, chest and abdomen. New data on the first modern, systematic study of the prevalence of aortic dissection in TS was presented. The estimated rate of dissection for all ages was 6-fold higher than the general population. Thus, the critical importance of visualizing the entire length of the thoracic aorta and the need for everyone with TS to have a MR study was

solidly endorsed by the entire conference. In addition to abnormal anatomy and compliance localized to the thoracic aorta, other major vessels also demonstrate distortion of normal structure and dilation and altered dynamic properties.

The finding of vascular distortion in very young girls and multiple sites was viewed as consistent with a connective tissue disorder phenotype, and hence comparison with Marfan syndrome, and consultation with experts in non-TS dissection pathology. In consideration of this analogy, new recommendations concerning caution with regard to extreme exercise and pregnancy were advanced, after considerable debate. Specifically, some experts thought that the potential danger of highly strenuous, competitive sports or isometric exercise was theoretically worrisome enough to justify explicit recommendation to avoid such activity, at least for those known to have aortic disease. Likewise for contemplation of pregnancy, recent reports emphasizing case reports and a possible 2% prevalence of aortic dissection and death among pregnant TS women led some discussants to categorically argue against pregnancy for most women with TS, while others felt that the 2% prevalence was not objective, and that discouraging exercise and pregnancy would over-medicalize the condition of young women with TS and exacerbate a tendency toward inertia and depression. The bottom line, endorsed by all participants, was that individuals with TS contemplating a new, strenuous exercise program or pregnancy need a full and comprehensive cardiovascular evaluation by a cardiologist with MR imaging.

In addition to new imaging recommendations, new findings on abnormal cardiac conduction and repolarization in girls and women with TS were presented and combined with recent findings of altered heart rate variability, seem to support a fundamental alteration in autonomic nervous system activity in TS. The baseline tachycardia and prolonged QTc in many patients with TS thus deserves closer evaluation to determine whether they may be at risk for arrhythmia.

In the field of pediatric growth and development there are also new recommendations. With the recent publication of the randomized, placebo-controlled Canadian GH in TS study, there is finally definitive evidence that GH promotes several inches of statural growth in the average girl with TS. The major determinants, or predictors, of final adult height were identified as height at start of GH use, dose and duration of GH use, and maternal origin of the single normal X chromosome. There was discussion on the optimal age of initiation, and duration of GH use, but these issues require further study. It was concluded, however, that delay of puberty to promote additional statural growth during the teen years was generally not advisable, since growth actually has been shown to continue unimpeded with the initiation of physiological estrogen treatment. Moreover, some evidence suggests that delay of pubertal development may aggravate the tendency to poor self-esteem, shyness and social anxiety affecting a substantial number of girls and young women with TS.

The section on psychosocial development emphasized the point that full scale intelligence is normal for most individuals with TS and that educational attainments are on the whole excellent. Specific problem areas have been identified, including difficulties with attention span, visual-spatial perception and some aspects of executive function (e.g., multi-tasking). Difficulties with social adjustment may manifest during childhood and adolescence, but adults with TS seem relatively stable in psychological terms. Again, major psychosocial issues seem to involve concern about ovarian insufficiency and what it means

for a women's view of her role in society and the consensus was that open and sensitive consideration of these issues in partnership with the patients is an important step toward addressing these feelings.

During adult life it is by now clear that morbidity is raised and new Danish data confirm British data showing that mortality is 2–4 fold increased. The importance of continued proper female hormone replacement therapy (HRT) is slowly being documented, with positive effects on liver function, blood pressure, aortic elasticity, bone metabolism, and possibly cognitive function. Especially the quite large effect on blood pressure with reductions in 24 h blood pressure equivalent to the effect by many antihypertensive drugs is important. However, there is a need to document the effect of HRT in long term longitudinal studies, and hopefully also address positive or negative effects on cancer incidence. Cardiovascular issues remain important during adult life, and long term studies are needed to address several questions like what anti-hypertensives to use, the rate of dilation of the aorta, as well as the effect of different HRT regimens (transdermal versus oral). Osteoporosis is frequent, but seems easily to be avoided when proper HRT is prescribed. However, we still need long term confirmation of the positive effect of HRT on bone metabolism. Ovarian function and thus infertility is being addressed in on-going studies in Sweden where ovarian biopsies are being studied, both for immediate cryo-preservation (for later transplantation) and for research purposes. It will prove important to elucidate the factors responsible for the accelerated apoptosis of follicles in TS.

Type 2 diabetes is frequent, and may depend more on diminished beta cell reserve than traditional insulin resistance, but further studies are needed to fully understand the nature of diabetes in TS, and also to possibly prevent the development of diabetes.

Hearing problems and the need for hearing aids, remain an agonizing and therefore important health complaint for many women with TS. In studies of quality of life, decreased hearing comes through as a very important cause of diminished quality of life. So far, the exact etiology behind has not been elucidated.

New international guidelines were prepared and are presently submitted to peer review and will serve as an update of guidelines previously published in the *Journal of Clinical Endocrinology and Metabolism* 2000.

The present book gives all speakers at the conference the possibility to present their latest contribution in detail. At the conference recent advances in the diagnosis and treatment of Turner syndrome was addressed.

In summary, we focused on 5 major areas of interest:

- Clinical genetics, where the need for information of parents of a fetus or newborn diagnosed with TS and their need of information describing the broad spectrum of TS phenotype and outcomes, and the normal quality of life reported by many individuals with the syndrome in recent years was discussed. Furthermore, the possibility of screening of high risk population or even the entire population for sex chromosome aberrations was discussed.
- Growth and Development, where recent studies describing the efficacy of growth hormone treatment begun early enough to increase adult height by several inches, but also that delay in pubertal development to further increase height may not be advisable.

- Psychosocial Development, where the increased risk for learning and attention deficit disorders in girls with TS mandates a comprehensive psycho-educational evaluation in early childhood or upon diagnosis.
- Congenital Cardiovascular Disease, where new areas in management include a more comprehensive evaluation of the cardiovascular system including a magnetic resonance study. Since a congenital affliction is pervasive throughout a lifetime, more aggressive blood pressure control and caution in regard to pregnancy and certain types of exercise for those with certain cardiovascular defects must be adhered to.
- Adulthood, where adults with TS need continued attention to congenital cardiovascular issues, i.e., aortic enlargement and blood pressure control. The importance of continued ovarian hormone treatment for adults with TS, at least until age 50 or so, needs to be reinforced, since the risk for severe osteoporosis in these women in a hypogonadal state is very high. Many adults with TS have multiple risk factors for atherosclerotic disease, hence early lifestyle counseling and monitoring for and intervention in hypertension, diabetes and dyslipidemia are advised.

It is our hope that the present book will serve as an inspiration for researchers, as an update and clinical guide for clinical working physicians, and as a source of information for parents and females with Turner syndrome.

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