

COMMENTARY

Care of adult women with Turner syndrome: the state of affairs in Germany

Mette H Viuff¹ and Claus H Gravholt^{1,2}¹Department of Molecular Medicine, Aarhus University Hospital, Aarhus, Denmark²Department of Endocrinology, Aarhus University Hospital, Aarhus, DenmarkCorrespondence should be addressed to C H Gravholt: ch.gravholt@dadlnet.dk

Abstract

In this commentary, we discuss the state of affairs concerning the clinical care of females with Turner syndrome (TS) in Germany. TS is a rare disease and new international guidelines describe an appropriate setup for optimal clinical care. Several countries have implemented a program with centralized adult Turner syndrome clinics, which are now found in France, Denmark, the Netherlands, Sweden, parts of England and possibly other countries, but hitherto not in Germany. Such an approach should ensure the availability of high quality multi-disciplinary care for all women with TS to be treated and to detect all the conditions that have been associated with TS, which typically appear at odd times during the lifetime of a female with TS. Care should be offered at no added cost for the patient, and treatment with relevant drugs should be available at reasonable cost for the individual patient. Currently, it is quite problematic that many female sex hormone preparations are not available at low cost in a number of countries. Additional problems include supply chain issue which lead to patients not being able to buy their usual drug for a certain period of time. We think it is timely that countries improve the care for individuals with rare conditions, such as TS.

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Turner syndrome (TS) is a condition with a missing X chromosome (45,X) or parts thereof or with a mosaic setup (45,X/46,XX or other variants). It is a rare disease. New international guidelines describe an appropriate setup for optimal clinical care (1). Several countries have implemented a program with centralized adult Turner syndrome clinics, which are now found in France, Denmark, the Netherlands, Sweden and parts of England and possibly other countries. This should ensure the availability of high-quality multidisciplinary care for all women with TS to be treated and to detect all the conditions that have been associated with TS, which typically appear at odd times during the lifetime of a female with TS. Care should be offered at no added cost for the patient, and treatment with relevant drugs should be available at reasonable cost for the individual patient. Currently, it is quite problematic that many female sex

hormone preparations are not available at low cost in a number of countries. For example, transdermal drugs such as gels or patches are not available in all countries or are only available at high costs. Additional problems include supply chain problems that many times lead to patients not being able to buy their usual drug for a certain period of time.

When the child with TS has finished treatment in the pediatric department, usually consisting of growth hormone treatment for promoting linear growth and induction of puberty to ensure appropriate development of secondary sex characteristics and neurocognitive development in line with peers, transitioning to an adult care taker will take place. This sounds like an easy task. However, in relation to TS, as is the case in relation to many other rare and even common conditions as well, transition has proven to be troublesome, and several

studies have documented that many patients ‘disappear’ in an apparent gap between pediatric and adult care (1, 2, 3).

It is also well documented that many patients will have undetected morbidity, which is only diagnosed once they are seen at a dedicated multidisciplinary clinic (4, 5, 6). Although it may at first glimpse seem easy to care for females with TS – ‘would one not just have to substitute the missing female sex hormone?’ you might think. The reality is that many times it can be exceedingly difficult. This is because TS is a *syndrome* – and as is the case with any other syndrome, lots of other conditions, diseases, socioeconomic circumstances, neurocognitive and psychological challenges, issues with fertility, and the frequent need for ovarian egg donation, makes its necessary for the anchor person (being the pivotal physician) to be able to achieve a holistic picture of the condition. In other words, this anchor physician is the pivotal physician who coordinates care, most often an endocrinologist, needs to have a comprehensive understanding of the syndrome and should be willing to take on this obligation (7). This, in order to direct the patient to the services that can be needed in another medical specialties (8).

Why is diagnosis of TS many times so tricky? Well, for one, most physicians still have the textbook image of a prototypical girl or woman with TS in the back of their mind and think that they can easily diagnose all females they encounter with possible TS. By now, however, numerous papers clearly show that this is not the case. In epidemiologic studies of TS the average age at diagnosis is around 15 years (9), and only rather few are picked up by prenatal screening programs (10). In a large clinical study, the average age at diagnosis was not much lower, but was dependent on karyotype – 45,X females typically being diagnosed earlier (11), while in another clinical study from Australia the median age at diagnosis was also 15 years (12). This illustrates that diagnosis is much more difficult than many clinicians believe. Our current approach, which is dependent on presenting clinical features which in turn leads to referral to a pediatrician, does not work, and many females with TS are only diagnosed during adult life. This leaves some adult TS on a diagnostic odyssey, especially those with an atypical phenotype, which is frequent among those only being diagnosed late, because adult caretakers are not that familiar with diagnosing TS. In fact, we think the only diagnostic avenue in the future will be to include TS, along with other sex chromosome abnormalities, in neonatal screening programs (13). This would allow complete diagnosis of TS without diagnostic delay.

In the November 2019 issue of *Endocrine Connections*, a paper was published on the current state of affairs in Germany in relation to adult care of TS (14). This paper paints a rather gloomy and grim picture of current standards of care for adult women with TS. We think the authors should be commended for publishing their results and their analysis of why it is so in Germany. It is not that we should think that Germany is an especially dark spot on the international horizon of care for patients with rare diseases, but rather that this case illustrates many of the problems that one is faced with when attempting to build a national and reputable service for an under-served patient population. The authors retrospectively document in five non-university endocrine centers in Germany that adult care was focused on endocrine manifestations of TS, while clinical features including cardiovascular disease, renal and liver involvement, autoimmune diseases, hearing loss, and osteoporosis were not focused on. The authors do not even discuss neurocognitive assessments, which often would not have been performed. In essence, this report shows much the same results as other previous retrospective analyses in other countries concerning the level of care (3, 4, 5, 12, 15, 16).

Surprisingly, karyotype was present in only 50% of the investigated cases. Since karyotype is essential for assessing the pattern of comorbidities, a verified diagnosis is essential to initiate or continue treatment. In order to avoid multiple karyotype testing, a possible solution could be establishment of a national cytogenetic registry, which is present in the Nordic countries, in order to retrieve the karyotype for further adult care, and importantly also, for research purposes.

Since mortality due to cardiac conditions is continuously elevated in Turner syndrome (17), the fact that only 43% underwent cardiac examination and only 8% had an MRI, shows that improvements are warranted. The new guidelines recommend that all TS individuals should be thoroughly investigated in order to prevent aortic rupture or progression of aortic stenosis and to avoid development of ischemic heart disease (1).

The authors also describe an initiative some years ago toward creating adult TS clinics in Germany, which did not become a success, for which the authors have no explanation. However, now there is another push in Germany for the creation of adult Turner syndrome centers, which was initiated in March 2019 and most likely will improve care for TS women in Germany. Much of the undetected additional morbidity being diagnosed in dedicated TS clinics should be preventable

with appropriate education of patients and physicians alike. In addition, Kahlert *et al.* found that up to 20% of their surveyed TS females were not receiving hormone replacement therapy, which is likely *the* treatment with the greatest health benefit in TS (7, 14). In a recent nationwide study in Denmark, we also identified non-treatment with hormone replacement therapy as being present in varying percentages of patients depending on karyotype (18) and furthermore documented more pronounced morbidity among non-users. The report by Kahlert *et al.* deals with 258 adult females with TS (1.6% of all women with TS in Germany) out of a combined population of an estimated 16,000 women with TS in Germany, and an estimated 115,000 women with TS in the EU (14). Suffice to say, currently only a fraction of these women has even received a diagnosis! In other words, there is a pressing need for better, more systematic care of TS, but also EU-wide and preferably world-wide registries in order to better collect comprehensive longitudinal data on individuals with TS concerning genotype-phenotype relations in an international setting. Many hypotheses could and should be tested in such a setting.

The creation of European Reference Networks (ERN), and especially the European Reference Network on Rare Endocrine Conditions (ENDO-ERN) within the EU, should prove to be a leveraging mechanism for ensuring equal level and accessibility of care, as well as quality of life, fertility, optimal care etc., promote cross-border research within the EU (and eventually also outside of the EU) in basic mechanisms and other aspects of TS, as well as other disorders of sex development (DSDs) (19).

In conclusion, the paper by Kahlert *et al.* highlights the overall problematic state of the current level of care for adults with TS within the EU, but probably even more pronounced outside the EU except perhaps a country like Australia, and the need to implement nationwide programs.

Declaration of interest

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

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Author contribution statement

M H V and C H G wrote this editorial together.

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