MANAGEMENT OF ENDOCRINE DISEASE: Transition of care for young adult patients with Turner syndrome

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Abstract

Turner syndrome (TS), affecting 1/2000 to 1/2500 live born girls, is a chromosomal aberration with a total or partial loss of one of the X chromosomes. The diagnosis can be established from the intra-uterine life to adulthood. TS is a chronic disease with particular morbidity and mortality. The loss to follow-up rate, during transition, between children and adult units, remains a crucial issue.

This review focusses on the adolescent and young adult patients with TS. The different goals of TS transition are presented as well as some of the tools available in order to improve this transition. The involvement of the patient's family, advocacy groups and therapeutic educational programs are discussed. A specificity concerning TS transition, as compared to other chronic diseases, relies on the fact that patients with TS may present a peculiar neurocognitive profile. They are in general more anxious than the general population. Therefore, psychological support should be offered to optimize transition.

Data illustrating the beneficial impact of an organised transition of TS, from paediatric units to multidisciplinary adult care systems, within the same reference centre are presented. Further studies are required to evaluate the mid to long term transition of paediatric patients referred to adult units.

Introduction

Transition is defined by the Society for Adolescent Medicine as a « purposeful, planned movement of adolescents and young adults with chronic physical and medical conditions from child centred to adult oriented health care system » (1). Most studies on transition have evaluated immediate transfer from paediatric units to adult units. However, mid to long term transfer in adult health care system of paediatric patients, should be assessed.

Turner syndrome (TS), affecting 1/2000 à 1/2500 live born girls, is a chromosomal aberration with total or partial loss of one of the X chromosomes (2, 3). Short stature and primary ovarian insufficiency (POI) are classic features of TS. The prognosis is mainly related to cardiovascular diseases, involving congenital heart diseases, hypertension, aortic dilatation and potential aortic dissection (4).

Recommendations to standardize TS medical care and follow-up have been initially published in 2001, followed by American guidelines and more recently international guidelines (5, 6, 7). The most recent was established following a meeting in Cincinnati, sponsored primarily by the European Society of Endocrinology (ESE) and co-sponsored by the PaediatriEndocrine Society, the European Society of Paediatric Endocrinology (ESPE) and the Endocrine Society (ES) (7).

Different modes of transition of patients with TS from paediatrics to adult units

In the nineties, the group of KR Rubin has proposed several modes of transition for patients with TS (8). The first one is a vertically integrated care model, with paediatric and adult units within the same hospital. It offers the advantage of providing a more simple transition and exchange of health care information from paediatric to adult care by sharing similar physicians, a familiar hospital to the transitioning patient, and the same electronic health records. In the second model, patients have access to paediatric and adult cares within the same health care system but not in a same site of care. The last

model involves distinct paediatric and adult care systems. To date, around the world, many patients with TS do not have access to an integrated paediatric-adult multidisciplinary care program.

Studies evaluating TS transition

A lack of appropriate transition for patients with TS has been reported in several studies conducted in Belgium, Australia, France and Poland (9, 10, 11, 12). The largest study included 568 women with TS, with an average age of 22.6 ± 2.6 years (range 18.3-31.2) (11). Only 3.5% of patients with TS underwent all recommended assessments within the 4-year period and 16% had undergone none of the recommended assessments. Multivariate analysis identified the type of physician, as the only factor associated with a better follow-up. This study illustrated the role of endocrinologists, in transition of patients with TS.

What are the key messages to be delivered to patients with TS during transition?

Several visits are usually necessary as many messages need to be delivered to the patient.

The karyotype

A special time should be dedicated to delivering the patient's karyotype. A study from the Turner Syndrome Life Course Project, including 656 women with TS, has recently reported a karyotype-phenotype analysis (13). The authors mentioned that the most common karyotypes are the classical monosomy (45,X: 41.6% of participants) and the 45,X/46,XX mosaicism. Patients with a ring X chromosome (45,X/ 46,X,r(X): 7.3% of participants) were more likely to have a metabolic syndrome, elevated liver enzymes and higher HbA1C than patients with the classical 45,X karyotype. This study suggested that follow-up of patients with TS could be stratified according to their karyotype. However, according to the international recommendations for the care of patients with TS, information concerning the long term follow-up should be given to all patients with TS, irrespective of their karyotype (7).

Hormonal replacement therapy

As the majority of patients with TS will experience primary ovarian insufficiency (POI) (6, 14), a goal is having patients comply with taking hormonal replacement therapy (HRT), including estrogens and progestins, up to the age of 50 (15). The positive benefit-risk ratio of HRT on skin, bone and heart function should be discussed (16). An important issue is to define with the patient the route of HRT, with oral or transdermal estrogens (15). Assessing whether the patient wishes or not to have withdrawal bleedings should be taken into account.

Bone density

Measuring bone density can be helpful in convincing patients about the benefits of estrogens. A recent Australian study has evaluated retrospectively bone density and bone fractures, in an adult population of 76 patients with TS. Despite a median age of 29 years, odds ratio of low bone mass in patients with TS was 9.8 times that of age- and gender-matched controls (17). In this study, the prevalence of non-continuous HRT was high as it reached 40% of the population.

Reproduction

Initially, the physician should take into account the cardiac phenotype and the aortic diameters, as a pregnancy may be contra indicated in some patients with TS with cardiovascular diseases (7). If Y chromosome material is present in the karyotype, bilateral gonadectomy should be discussed in order to reduce the risk of gonadoblastoma (7).

If the patient is still spontaneously menstruating, information should be given that the rate of spontaneous pregnancy is around 6% (18). In such patients, oocyte cryopreservation should be proposed. Indeed, mature oocytes may be obtained after ovarian stimulation. The oocytes are retrieved by transvaginal retrieval and then vitrified for fertility preservation. No pregnancy has been reported, so far, after using cryopreserved oocytes, in patients with TS. When this technique is performed, because of age or non-oncological medical conditions, more than 10 to 12 oocytes are necessary to

obtain a pregnancy (19). Therefore oocyte cryopreservation does not apply to patients with TS, when their ovarian reserve is too low.

In some cases, ovarian tissue has been preserved during childhood, before the occurrence of POI. No pregnancy has been reported, so far, in patients with TS after using frozen ovarian fragments. Furthermore, the potential impacts of ovarian tissue freezing performed during childhood, on oocyte competence remains quite unknown. Few studies have evaluated such oocyte competence in patients with TS (20, 21, 22, 23, 24). Genetics of 11 oocytes obtained in ayoung woman with TS (23) have been evaluated by fluorescent *in situ* hybridization analysis. Among them, none had chromosomal abnormalities. Although this study is rather reassuring, few data are available concerning fertility preservation techniques in patients with TS. A single live birth has been reported, after autograft of ovarian tissue cryopreserved during childhood, in a patient with sickle cell anaemia (25). A single case of live birth after allografting of ovarian cortex between monozygotic twins with TS (45X, 46XX) and discordant ovarian function has been reported (26).

In case of POI, patients should be oriented towards oocyte donation programs. However, repeated careful cardiovascular evaluation is necessary.

Cardiovascular follow-up

During transition, cardiovascular status needs to be re-evaluated (4, 27). The need of a long term follow-up of aortic dilatation by cardiac magnetic resonance imaging (CMR) and/or transthoracic echocardiography (TTE) has to be explained. The frequency of cardiovascular evaluation is decided according to the initial aortic diameter at the age of 16, and the presence of associated cardiovascular risks such as aortic coarctation, hypertension and bicuspid aortic valve. According to the international guidelines, it ranges from every year to ten years (7).

The main difficulty with TS transition lies in the multiplicity of the necessary exams. Care in adults includes evaluation of liver function, lipid and glucose levels, bone density, audiometric, ophthalmologic and dermatological evaluations as well as autoimmune screening, essentially for thyroid and celiac disease (7). Hearing problems are frequent and are associated with poor quality of

life and social isolation. Motivating patients for their lifelong follow-up is a major issue of mid to long term transition.

What are the tools available in order to improve TS transition?

A tool for the transition readiness assessment is provided by The Endocrine Society. It includes 10 questions about health, 16 questions about using health care and 15 questions concerning social and emotional factors. A provider assessment of skill test, a clinical summary and transfer record, as well as a recommended approach for transitioning into adult practice are available on the website, (http://www.endocrinetransitions.org).

Partners of choice in the field of non-medical actors are advocacy groups (28) (CAIRN.Info). Several of them are involved with TS, such as the Turner Syndrome Support Society in the UK (tss.org.uk), the Turner foundation (turnersyndromefoundation.org) or the Turner Syndrome Society of the United States in the USA (turnersyndrome.org) and AGAT in France (agat-turner.org), or in other countries (please see Orphanet links). Parental and family involvements are crucial for a successful TS transition.

Therapeutic education or personalised care planning may potentially increase the transition's success rate (29). Among endocrine disorders, the most common chronic diseases where transition has been particularly studied are diabetes (30), 21 hydroxylase deficiency (31, 32) or hypopituitarism (33). A Cochrane review on personalised care planning has shown that the effects are not large, but they appear greater when the intervention is more comprehensive, more intensive, and better integrated into routine care (34). Our unit has developed a dedicated therapeutic education program for adult patients with TS. The goal of this program is a pragmatic approach for defining competencies and resources. Each session includes 3 to 5 patients and lasts one day, from 9 am to 4 pm. Patients come from all over France. A nurse trained for therapeutic education performs upon the patient's arrival, an educational diagnosis. Thereafter, a series of four thematic workshops, eaclasting 1 hour, is performed by physicians from the unit (an endocrinologist, a gynaecologist and a psychiatrist). The workshops deal respectively with feminine, dietary, somatic and psychological issues, related to TS. The

discussions during each session are initiated by a homemade educational map (Figure 1). Each patient shares her own experience with her peers. At the end of the day, patients complete a knowledge assessment on TS. Then, the nurse establishes future targets in order to improve the acceptance of the disease and educative competencies (Supplemental Table 1). We are planning to include expert patients, during those sessions.

Specificity of the transition of patients with TS

A major issue in organising TS transition is to take into account the psychology of those patients. Adolescence has been thought to be a high-risk period for girls with TS given their delay in pubertal and linear growth. Furthermore, TS is associated with a peculiar neurocognitive profile. In general, patients suffer from an excessive dissatisfaction with self-image and self-esteem (35, 36). Girls or young women with TS are less socially active than unaffected girls of similar age, in terms of time spent with friends or number of friends. This poor adolescent psychosocial integration is explained by a negative body image (37) and in some cases poor family acceptance of the diagnosis (38). Furthermore, attention deficit hyperactivity disorders (ADHD) are more frequent in TS. A recent study has reported an increased rate of 24% of ADHD in patients with TS, as compared to 1.3% in the general population (39). Therefore, some patients may have specific intellectual difficulties such as organizational, planning or task prioritization disorders (40). A psychological support is important to enhance the patient's self-esteem, and to reach a satisfactory quality of life level thus optimizing transition (41).

On the other hand, inflexibility and preoccupation with keeping things in order are often reported in patients with TS (36). Those characteristics should be an advantage, as they should improve compliance for the mid and long term follow-up, when immediate transition has been successful.

Results of TS transition in our centre

In order to illustrate this review, we evaluated TS transition in adult patients, followed in our unit, in Saint-Antoine Hospital, Paris, France (Figure 2). Our unit belongs to a center of rare diseases, which includes children as well as adults units. It has been labelled by the French Ministry of Health in 2006. It is a member of the European Reference Network on Rare Endocrine conditions (Endo-ERN). Among the 258 patients in our adult unit, 220 (85.3%) have been diagnosed with TS before the age of 20 years. Among those, we distinguished patients who had an "organised transition", therefore coming directly from paediatric endocrine units (n=112) from patients referred by their general practitioner, their gynaecologists or coming spontaneously to our unit (n=108). In order to evaluate if the transition had been successful, each patient's electronic file was studied. The frequencies of visits and/or day hospitals were evaluated. Transition was defined as successful if the patient, after an initial visit, came in our unit, at least once, over the past 4 years. This figure was chosen, according to the mean frequency of cardiovascular evaluation, as recommended in the international guidelines (7). As shown in Figure 2, the mean age at TS diagnosis was similar in both groups. However, the percentage of patients lost to follow-up was statistically lower among the patients referred directly by paediatricians from our reference centre ($p < 5x\ 10^{-13}$ using a Fisher test). Age at first visit in the adult unit was older in the group without transition, illustrating a lack of follow-up. Although many biases may be present in this evaluation, a paediatric diagnosis followed by a synchronized adult follow-up using a common file was associated with a less frequent loss to follow-up and a higher frequency of visits performed in our adult reference centre. A remaining challenge is to understand why some patients and/or their family have not transferred directly from the paediatric care, where TS was initially diagnosed and followed. A recent review identified the barriers to transition from paediatric to adult care (42). The most common fall within the relationship domains, followed by access/insurance and belief/expectations. Carel *et al.* has shown previously that most socially vulnerable patients may be the one who will be lost at follow-up (11). However, the cost of care should not be involved in the success of transition in our evaluation, as in France full reimbursement of the patient's care is provided for every patients with TS.

Conclusion

Not so long ago, most young adults with TS were making their way through the healthcare system in an uncoordinated way (1). Hence, inequity of care would affect patients already bearing the burden of a rare disease. A successful health care transition should help other aspects of life, such as work, school, or other social issues (). Young adults with a chronic rare condition like TS need a multidisciplinary approach to their care plan, including psychosocial aspects. Our preliminary data are in favour of an organised transition from paediatric to adult care units, within the same reference centre of rare diseases. Further studies are necessary in order to evaluate failure of transition, essentially the social and/or psychological characteristics of patients with TS.

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Figure legends

Figure 1. Educational map

During the therapeutic education program, each patient with TS shares her own experience with her peers thanks to a homemade educational mal. Feminine, somatic and psychological questions related to TS are discussed.

Figure 2. Evaluation of transition in adult patients with TS followed in Saint-Antoine Hospital (Paris, France)

Among the 258 patients in our cohort, 220 (85.3%) have been diagnosed with TS before the age of 20 years. Among those, 112 have transitioned directly from paediatric endocrine units belonging to our reference centre whereas 108 were addressed indirectly. The number of patients lost to follow-up was statistically lower among the patients referred directly by paediatricians (0/112) versus those who were not (35/108) ($p < 5x\ 10^{-13}$ using a Fisher test).

FIGURE 1.

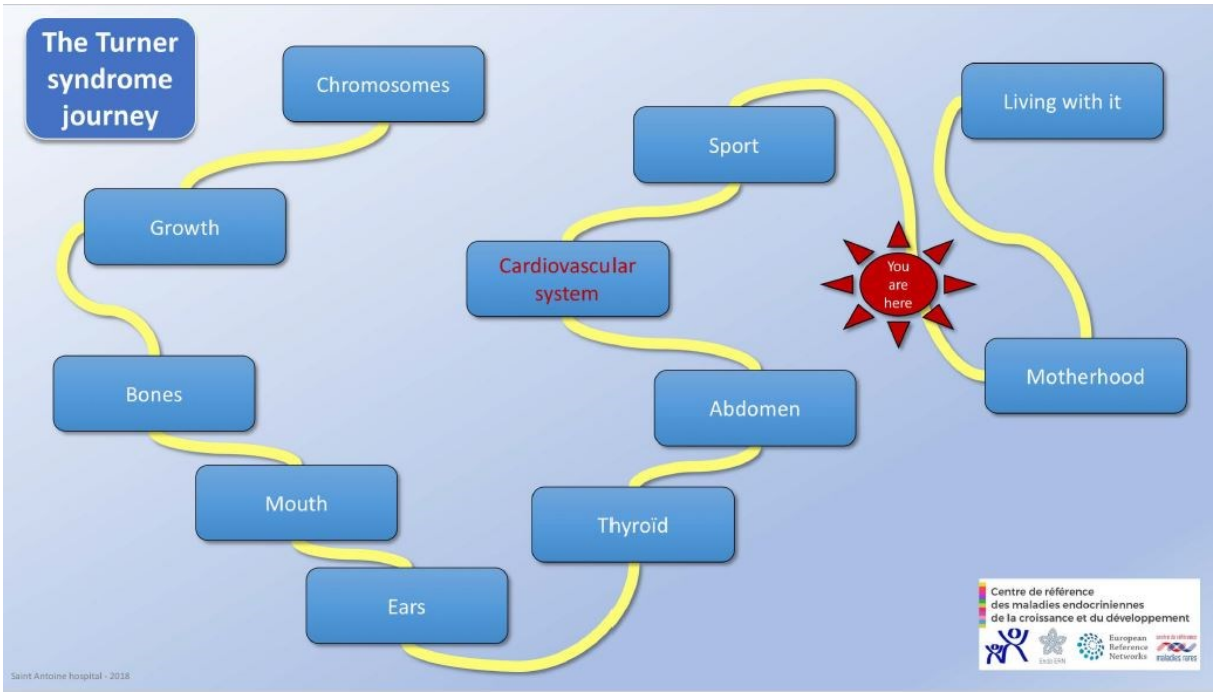
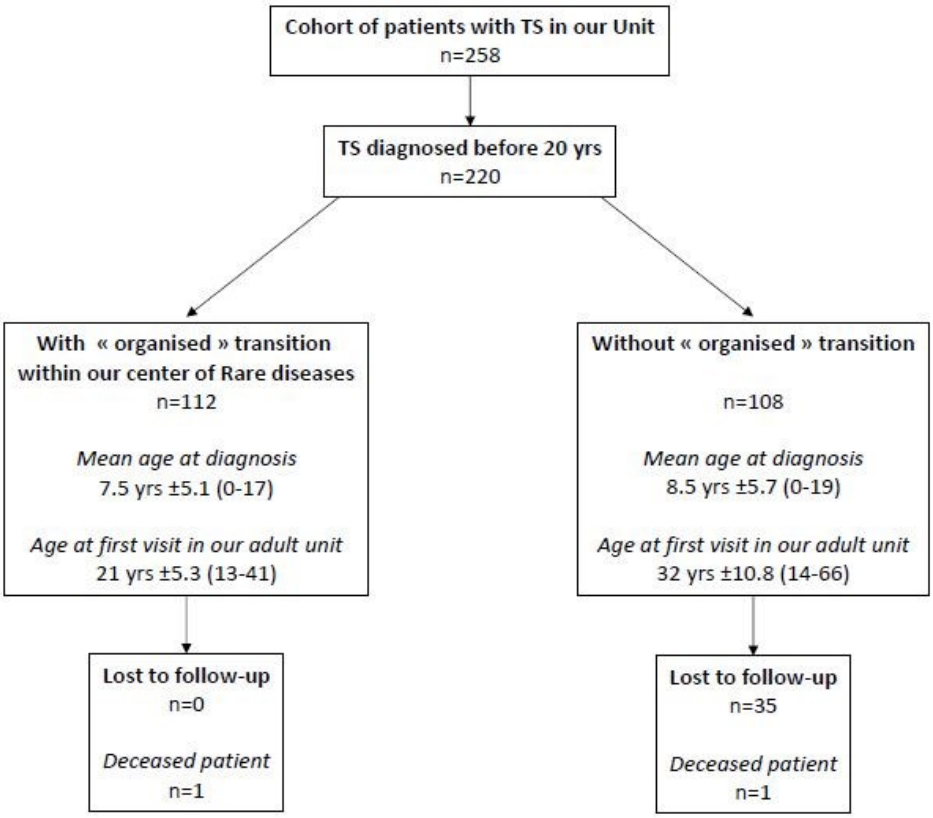

The Turner syndrome journey
Chromosomes
Growth
Bones
Mouth
Ears
Thyroid
Abdomen
Cardiovascular system
Sport
You are here
Living with it
Motherhood
Centre de référence des maladies endocriniennes de la croissance et du développement
European Reference Networks
Saint Antoine hospital - 2018

Figure 2.


Cohort of patients with TS in our Unit
n=258
TS diagnosed before 20 yrs
n=220
With « organised » transition within our center of Rare diseases
n=112
Mean age at diagnosis
7.5 yrs ±5.1 (0-17)
Age at first visit in our adult unit
21 yrs ±5.3 (13-41)
Without « organised » transition
n=108
Mean age at diagnosis
8.5 yrs ±5.7 (0-19)
Age at first visit in our adult unit
32 yrs ±10.8 (14-66)
Lost to follow-up
n=0
Deceased patient
n=1
Lost to follow-up
n=35
Deceased patient
n=1