FOLLOW UP FOR ADULTS WITH TURNER'S SYNDROME

- *www.tss.org.uk*
- *NEJM 2004;331:1227*
- *Endocrine Reviews 2002; 23:120.*
- *JCEM 2001; 86:3060.*

It is generally suggested that all adults should be under the care of a specialist (multidisciplinary) TS clinic because of:

- A 3 fold increased overall mortality with life expectancy reduced by 13 years, mainly due to cardiovascular deaths (aortic root rupture, CHD).
- Long term specific medical problems.

Follow-up scheme:

Fist visit/Baseline data which should be available/obtained, in addition to 'annual visit' data:

- Karyotype
  - Y –chromosome material?
- Renal and pelvic ultrasound
- Gonadotrophins

Annually

- Examination (BMI, BP, CVS, etc)
- Thyroid function.
- *Fasting* plasma glucose, lipids
- Liver function
- Renal function

5 yearly

- Echo (MRI is used in some centres)
- DEXA
- Audiogram *(see discussion for changes in this intervals)*

Note: The Turner syndrome support society offers useful information and support to patients.

Discussion

These guidelines are in agreement with those produced by the Turner's Syndrome Support Society, and 'expert' groups.
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Cytogenetics

All patients should have their karyotype recorded. This is important to ensure there is no Y-chromosome material present (see below) and because there are genotype phenotype correlations. (Although these are not clinically useful at the moment, but may become so in time with better follow-up of large cohorts of patients.)

Cytogenetics of 196 women attending the Adult Turner clinics at the Middlesex and Oxford Radcliffe hospitals, UK, and correlation with phenotype:

Karyotype	No.	%	Phenotype
45,X	95	48	Most severe phenotype. Highest incidence of structural cardiac and renal abnormalities.
46,Xi(Xq)	36	18	Structural abnormalities uncommon. Increased risk of autoimmunity, particularly thyroiditis and IBD, and deafness.
45,X/46,XX	21	11	Least severe phenotype. Increased mean height. Spontaneous puberty and menses in up to 40%.
46,Xr(X)	19	10	Spontaneous menses in 33%. Congenital abnormalities uncommon. Cognitive dysfunction in those with a small ring chromosome.
45,X/46,XY	11	6	Increased risk of gonadoblastoma.
45,X/46,X,idic(Y)	2	1	Increased risk of gonadoblastoma.
46,XXp-	3	1.5	Similar phenotype to 45,X monosomy.
46,XXq-	6	3	Variable phenotype.
other	3	1.5	

Gonadoblastoma

- Patients with Y-chromosome material on conventional karyotyping are at increased risk for developing gonadoblastomas.
- Risk increases with age: 2% at 10 years, 28% at age 30.
- Malignant transformation in 60%.

Recommendation:

- Routine gonadectomy before puberty.
- Follow up with ultrasound and colour flow doppler in non-gonadectomised.

Note: 5% of patients with Turner's have low levels Y-mosaicism with Y material detected by PCR.

- Clinical significance uncertain, routine screening not warranted.
- Consider PCR if virilisation or unknown marker chromosome as the chance of 'significant' Y material present is large.

Other neoplasms

Two retrospective series suggest an increased incidence of **colon cancer** (5 to 7 fold increased risk), but this 'evidence' should be counterbalanced against a general paucity of reports otherwise. Risk factors for colon cancer include inflammatory bowel disease and oestrogen deficiency. Routine screening is currently not recommended.

The prevalence of **pigmented naevi** is increased at 27%. The risk of malignancy is however not increased. Remember that there is an increased risk of keloid formation when discussing surgical removal of naevi.

Renal disorders

25-43% of patients have significant structural abnormalities. This potentially predisposes them to infection, renal impairment and may contribute to HPT and renal structure should thus be clearly documented by ultrasound.

Abnormality	Incidence in TS
Double collecting system	5–11%
Horseshoe kidney	10–16%
Rotational abnormalities	6–8%
Ectopic kidney (including pelvic kidney)	2.5–3.5%
Absent kidney	2–5%
Ureteropelvic obstruction	3–5%
Aberrant blood supply	2%

Pregnancy

Although patients are nearly always infertile, spontaneous pregnancy is occasionally possible. It is important to have documentation of elevated gonadotrophins, particularly in patients who are mosaic or have had a spontaneous puberty or menarche.

It is recommended that women with TS receive cyclical estrogen and progestin. There is no specific evidence as to which type of replacement to use; the type, route of administration and dose should be individualized, taking into account patient preference, symptoms and co-existing illness. Sufficient oestrogen should be prescribed to prevent the symptoms, signs, and sequelae of estrogen deficiency. Most adult women with TS will require at least the equivalent of 2 mg 17β-estradiol daily. HRT preparations, with continuous deliver of oestrogen, may be preferable to the pill as many patients with TS develop symptoms of oestrogen deficiency in the pill-free week. The duration of HRT after age 50 should be made on an individual basis.

Spontaneous pregnancy in TS (? More common than this)

Karyotype	Subjects (n)	Pregnancies (n)	Healthy pregnancies	Abortions or stillbirths	Congenital or chromosomal abnormalities
45,X	16	32	14	15	3
Mosaic	49	104	39	39	26
Ring chromosome	7	12	5	1	6
46,Xdel(Xp)	3	6	1	2	3
Total	80	167	64 (38%)	65 (40%)	38 (23%)

Thyroid disease

In adults:

- 50% have positive thyroid antibodies – predictive.
- 30% hypothyroid.

Recommendations:

- Annual thyroid function tests. Thyroid antibodies to confirm diagnosis.

Otological disorders

About 15% of adults with TS experience significant hearing loss, which may be conductive and/or sensorineural. 25% of these patients benefit from a hearing aid. The sensorineural hearing loss, which is present in 50–90% of patients, consists of a sensorineural dip in the 1.5–2 kHz region and/or sensorineural high frequency loss. The hearing loss is progressive, but tends to occur rapidly after about 35 yr of age, leading to early aging with presbyacusis. Hearing aids are frequently necessary. If only a sensorineural dip is present, follow-up should occur every 5 years. Otological follow-up assessments can be conducted every 10 yr in patients who do not have hearing problems and whose karyotype is a low risk indicator for otitis media or a sensorineural dip [*i.e.* 45,X or 46X,I(Xq)].

Bone disease

Be aware of mechanical issues such as dislocated hips, scoliosis, osteoarthritis.

Osteoporosis in Turner's syndrome remains a controversial topic, particularly as good long term studies are not available. The validity of DEXA BMD is also discussed as patients have smaller bones and an appropriate reference range does not exist. From a pathophysiologic point of view, there is still debate whether osteoporosis is intrinsic to Turner's or purely secondary the hormonal disturbances.

The best current studies suggest a reduction in peak bone mass of 25% with a 10 fold increased risk of developing osteoporosis (based on historical data though, when oestrogen and GH replacement was not 'optimal'). Turner's seems to be associated with 2-3 fold increased risk of fracture, at least if not adequately treated with oestrogen. Two studies showed 16 and 46% incidence of fractures.

Current treatment for osteoporosis is optimal HRT. There are no studies on the use of bisphosphonates. There are no prospective treatment studies; the best we can do is be aware of the issue and follow-up on problems on an individual basis.

Cardiovascular disease

Congenital heart disease

Congenital heart disease (left sided abnormalities) is common. An ECHO would have been obtained at diagnosis, and should be repeated after puberty. It is important to remember that endocarditis prophylaxis is currently advised for patients with bicuspid aortic valves.

	No. (%)
Total no. of patients assessed	1,126
Structural abnormalities	
Bicuspid aortic valve	132 (12)
Coarctation of aorta	103 (9)
Aortic stenosis/regurgitation	38 (3.4)
Partial anomalous venous drainage of the pulmonary veins	26 (2.3)
Other	17 (1.5)
Total	316 (28)

Hypertension

There is a 3-fold increased risk of developing hypertension. This is currently considered to be a major contributor to increased mortality. 7 -17% of children and 24-40 % of adults are hypertensive. A secondary cause can be found in about 20% of patients (coarctation, renal disease). Use ACE-I with caution (the hypertension is thought to be due to renovascular small vessel disease).

Ischaemic heart disease

The risks of ischaemic heart disease is not well documented, but is considered to be about doubled. Risk factors include hypertension and insulin resistance and the role of oestrogen (replacement and/or deficiency).

Aortic dissection

This remains a controversial topic, because of the total absence of prospective studies. The prevalence of aortic root dilatation in different studies ranges between 8 - 46%. Patients with hypertension or coarctation are at increased risk.

Aortic dilatation and dissection in TS: a review of the literature

	No. (%)
Total no. of patients	70
No. of patients below 21 yr	33 (47)
No. of patients above 21 yr	37 (53)
45,X karyotype (data available for 44 cases)	36 (82)
No. with **structural cardiac abnormality**	50 (71)
No. with **hypertension**	32 (46)
No. with no risk factor	6 (8.6)
No. presenting with aortic dissection	44 (63)
Site of aortic dilatation/dissection	
Ascending aorta	29 (49)
Descending aorta	9 (15)
Both	21 (36)
Unspecified	11
Evidence of cystic medial necrosis (histology available for 25 patients)	18 (72)
Deaths	25 (36)

Problems:

- MRI/ECHO detect different patients and are complementary. MRI too expensive for routine use.
- Normal dimensions for TS aorta is not known – correct for height and BSA or use ratio aortic root:descending aorta.
- Natural history not known, nor is the effects of intervention. What is 'critical' dilatation, when surgery might be indicated?

Recommendation:

- At the moment it seems prudent to recommend an ECHO 5 yearly.
  - Also:
    - Aggresively treat BP
    - Consider beta blockers because of their proven track record for aortic protection in Marfan's syndrome. (There is no evidence in TS).
    - Manage cases with cardiology input.

Gastrointestinal disease

- There is a 2 – 3 fold increased risk of IBD. The prevalence is 2- 3% in TS.
    - Isochromosome Xq phenotype account for 52%.

- There is also an increased risk of hepatic disease.
    - Cirrhosis is five times increased. 40 - 80% of TS > age 35 have abnormal liver function tests.
    - Cause/ natural history not known:
        - ? developmental
        - ? autoimmune
        - ? NAFLD
        - ? relationship with oestrogen replacement
    - Consider using *transdermal* oestrogen.
- Intestinal telangiectasia is more common in Turner's.

Protocol prepared by Peter Raubenheimer: NEXT REVIEW: 2008