Optimising management in Turner syndrome: from infancy to adult transfer

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REVIEW

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Turner syndrome can be defined as loss or abnormality of the second X chromosome in at least one cell line in a phenotypic female. The condition occurs in approximately 1 in every 2000 live female births,[1] so that in the UK the prevalence for any year of life is in the region of 200 girls. The condition is much more common in utero, it being estimated that 1–2% of all conceptuses are affected, of whom only 1% will survive to term.[2 3]

While short stature and gonadal dysgenesis are the cardinal features of Turner syndrome (TS), affected girls may also encounter a wide range of problems from conductive deafness to schooling difficulties. The purpose of this review, therefore, is to systematically discuss the array of problems faced by affected subjects, and to outline their optimal management from infancy until 18 years of age—the usual time of transfer to adult services. Our recommendations are derived partly from the published literature and also from our experience with 150 families with TS seen at the Royal Hospital for Sick Children (RHSC) in Glasgow in the dedicated Turner clinic, which was founded in 1989.

The proforma is available on the *ADC* website (http://www.archdischild.com/supplemental)

See end of article for authors' affiliations

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GENETIC ASPECTS

The second chromosome may be completely lost (45,X), undergo duplication of the long arm (q) with concomitant loss of the short arm (p) to form an isochromosome (isoXq), undergo ring formation (rX), or deletion in the short or long arm (Xp− or Xq−). Complete 45,X monosomy accounts for 40–60% of the karyotypes on peripheral blood lymphocytes, while most of the remaining karyotypes show a mosaic pattern—for example, 45,X/46,XX, 45,X/46,XiXq, 45,X/46,XY, 45,X/46,XrX.

Two notable aspects of TS are the remarkable mildness of the condition, when one considers that part or all of one chromosome is missing from the cells; and the marked phenotypic variability between individuals. These features can partly be explained by the phenomena of X inactivation, genotypic variability, and the theory of occult 46,XX mosaicism.

Permanent inactivation of the second X chromosome takes place the end of the first week (at the 16–64 cell stage) and involves either the maternally or paternally derived X in a random fashion. However, if the X chromosome is abnormal, it will usually be preferentially inactivated, unless the inactivation centre (XIST) is itself impaired, as may occur in some cases of ring X chromosome. In the majority of girls with TS, the normal X chromosome is maternal in origin.[4]

Given that loss or abnormality of the second sex chromosome does affect the phenotype, it is implicit that inactivation must be partial rather than complete. This is indeed the case, especially for the genes located on Xp where up to 30% are not silenced, including those on the pseudoautosomal regions, in contrast to only 3% of the genes on Xq.[5] Genes involved with stature (for example, the SHOX gene), lymphatic development, naevus formation, and ovarian development are expressed on the X chromosome.[6–9] Variability in the inactivation of these genes leading to varying degrees of haploinsufficiency, especially in the pseudoautosomal regions, partly explains the variable phenotype.

The phenotype/genotype correlation in TS is generally poor. However, individuals with mosaicism for a normal cell line (45,X/46,XX) are mildly affected, as (surprisingly) are those with the unusual 45,X/47,XXX karyotype.[10] A 46,X,iXq cell line is associated with an increased risk of inflammatory bowel disease[11] and autoimmune thyroiditis,[12] while those with a ring or marker chromosome have a higher risk of learning difficulties.[13 14] Girls with Y chromosome material are at increased risk of gonadoblastoma[15] and gonadectomy is recommended. Those who have unidentified marker chromosomes should, therefore, undergo further testing for Y chromosomal material.

Finally, blood karyotype may not be representative of that in other tissue. It is hypothesised that the 1% of Turner fetuses surviving to term represent an ''elite'' with a critical mass of normal 46,XX cells necessary for survival—occult mosaicism.[16] Phenotypic variability could relate to differing degrees and tissue patterns of occult mosaicism.

MANAGEMENT

General considerations

Box 1 chronicles the natural history of TS from birth to young adulthood, detailing the problems that can be encountered. It is important to stress that many girls with TS experience few problems other than short stature and ovarian failure. It is clearly not possible for any single clinician to directly address all the needs of these patients. The responsible paediatrician—usually an endocrinologist—needs to be aware of the scope of problems, so that prompt referral to the appropriate services can be made as required.

Once the initial shock of the diagnosis has settled, patients and parents usually find the

Box 1: The natural history of Turner syndrome and its associated problems

Birth and neonatal period

- Growth: often borderline small for gestational age
- Lymphoedema
- Cardiac abnormalities: e.g. coarctation of aorta, aortic stenosis, bicuspid aortic valve

Infancy

- Growth: length—usually close to and parallel to the 3rd centile
- Feeding difficulties with weight faltering
- Poor sleeping pattern

Preschool

- Short stature: height velocity usually low/normal
- High activity levels
- Behavioural difficulties with exaggerated fearfulness
- Recurrent middle ear infections; otitis media with effusion (glue ear); variable conductive hearing loss; sensorineural deafness in a minority

School

- Growth: height—gradually falling away from 3rd centile
- Middle ear disease (see above)
- Obesity
- Specific learning difficulties: e.g. mathematics, visuo-spatial tasks
- Social vulnerability
- Foot problems: e.g. toenail involution, cellulitis
- Renal anomalies: e.g. horseshoe, duplex, unusually shaped kidneys

Adolescence

- Growth: impaired pubertal growth spurt even with oestrogen induction
- Ovarian failure: absent/incomplete puberty
- Obesity
- Hypertension
- Increased prevalence of immune disorders:
  - Autoimmune thyroiditis
  - Coeliac disease
  - Inflammatory bowel disease
- Specific learning difficulties
- Social vulnerability
- Foot problems

Young adulthood

- Need for counselling re:
  - Long term oestrogen replacement
  - Fertility
- Obesity
- Hypertension
- Aortic dilatation/dissection
- Autoimmune thyroiditis
- Osteoporosis
- Visuospatial difficulties
- Sensorineural deafness

variety of information booklets available from organisations such as the Turner Syndrome Support Society (www.tss.org.uk) and the Child Growth Foundation (www.childgrowthfoundation.org) extremely helpful. These now include booklets for older girls and teachers.[17–21] The family may find it helpful to meet a child of the same age or older with Turner syndrome—something that will happen naturally if the child attends a dedicated clinic. The monthly Turner clinic at RHSC Glasgow is attended by a multidisciplinary team of medical, nursing, and research staff and includes the consultant gynaecologist and obstetrician to whom the girls are eventually transferred when leaving paediatric services.

Although the management of individual patients is bound to be problem led, it is nevertheless important to adopt a systematic and pre-emptive approach to all patients. Table 1 outlines our recommended guidelines for monitoring and treatment. To assist in the assessment of patients at initial diagnosis, we have devised a detailed proforma (available on the *ADC* website; http://www.archdischild.com/supplemental), together with one for annual assessment. This ensures that aspects as diverse as educational status, monitoring of blood pressure, and thyroid function are not overlooked during the consultation.

Congenital heart disease

Cardiac abnormalities are found in up to 50% of patients.[22] Coarctation of the aorta usually presents in early infancy, requiring emergency surgery. Critical aortic stenosis occurs in a minority of patients[22] and is also managed surgically. Bicuspid (as opposed to tricuspid) aortic valve, the most common cardiac malformation (13–34% of patients),[23] is detected on routine echocardiogram. This finding merely requires surveillance and endocarditis prophylaxis.

We recommend cardiac referral and echocardiography at the time of diagnosis in TS, with re-evaluation at 10 years in girls who were diagnosed during the preschool years, when minor anomalies such as bicuspid valve may not have been identified. Reassessment is also suggested at the time of adult transfer (see Cardiovascular health, below).

Hypertension

During adolescence hypertension becomes prevalent. Over 30% of girls aged 5.4–22.4 years were found to be mildly hypertensive in one study[24] and over 50% had an abnormal blood pressure profile.[25] We recommend annual measurement of blood pressure from school age, plotting the value on an age specific chart (Jackson L, Thalange N, Cole TJ. Blood pressure centiles, girls, aged 4–24, personal communication). If the value is above the 98th centile, the family doctor is asked to repeat the measurement between clinics. If the value is still high, ambulatory monitoring is carried out. If sustained hypertension is confirmed, antihypertensive treatment is indicated.

Renal care

Structural renal anomalies, including horseshoe kidney, duplex systems, and long posteriorly rotated kidneys, are

Table 1 Proposed model of assessment and management for girls with Turner syndrome from infancy to 18 years

Measurements and investigations	Treatment
4–6 monthly Height and weight Blood pressure Pubertal staging (from 10 years onwards)	**Growth hormone** Age at start When height falls <−2 SD on a standard growth chart or When the family identifies short stature as becoming a problem or By 8 years of age Dose: 10 mg/m^2/week (≈0.3 mg/kg/week) by daily injection
12–18 monthly Thyroid function and IGF-1 measurement Bone age Hearing assessment	
3–5 yearly DXA scan for bone density	**Oestrogen for pubertal induction*** Age at start: 13 years, unless GH started particularly late and in the absence of any patient/family preference for earlier or later
Other assessments FSH levels and pelvic ultrasound scan prior to pubertal induction Liver function tests, prior to (a) pubertal induction and (b) adult transfer Renal imaging Ultrasound scan at diagnosis and at adult transfer. Additional imaging if indicated (e.g. ultrasound abnormal ± recurrent UTI) Cardiac assessment Ultrasound scan at diagnosis, at pubertal induction, and at adult transfer Eye assessment at diagnosis, follow up as required	Dose: Protocol adopted by UK Turner Study (see text for details): Year 1: Ethinyloestradiol 2 μg daily Year 2: Ethinyloestradiol 4 μg daily Year 3: Ethinyloestradiol 6 μg daily, increasing every 4 months to 8 μg and then 10 μg daily Year 4: Adult replacement dose Norethisterone 5 mg daily for the first 5 days of each calendar month when ethinyloestradiol reaches 10 μg daily, or when breakthrough bleeding occurs, whichever is the sooner
Referral as required ENT/Audiology Podiatrist Dietician Dermatologist Psychologist Ophthalmology	**Oxandrolone*** Age at start: from 9 years of age Dose: 0.05 mg/kg/day, maximum 2.5 mg/day

*Currently under investigation in the UK Turner Study.

common in TS with a prevalence of 33% in one study.[26] This figure may be higher in 45,X monosomy.[27] These anomalies are not linked with the development of hypertension,[24] and rarely give rise to clinical symptoms. We recommend simply carrying out a renal ultrasound assessment at diagnosis and repeating this at the time of adult transfer. We also have a low threshold for obtaining urine culture if the patient has urinary symptoms, including enuresis. However, we do not routinely culture the urine in clinic.

Box 2: Physical stigmata of Turner syndrome

- Borderline small for gestational age
- Short stature
- Short 4th/5th metacarpal
- Cubitus valgus
- High palate
- Dental overcrowding
- Micrognathia
- Broad "shield" chest
- Hyperconvex nails ± nail-fold oedema
- Neck webbing
- Naevi (especially facial)
- Ptosis, squint, hypermetropia
- Epicanthic folds
- Oblique palpebral fissures
- Low set, posteriorly rotated ears
- Low hairline

Liver function

Abnormal liver function has been reported in adults with TS,[28 29] with a fivefold increase in the risk of cirrhosis.[30] Data from children, however, are less conclusive. Raised liver enzymes have been reported in girls with TS,[31] although these can be transient and appear to be benign. We suggest that liver function tests are performed when blood is taken prior to pubertal induction, and then again prior to adult transfer.

Feeding difficulties

This is a variable problem, some TS infants experiencing no feeding difficulties while others develop weight faltering as a consequence.[32] The feeding difficulty is related to a combination of the high arched palate, dysfunctional tongue movements, and poorly developed chewing skills.[33] Input from the dietician, and speech and language therapist may be required during infancy and the toddler years, after which time the feeding difficulties tend to settle down.

Thyroid dysfunction

There is an increased prevalence of autoimmune thyroiditis in TS.[12] We have also observed mild and transient TSH elevation (6–10 mU/l) in the absence of thyroid autoantibodies. Thyroid function should be checked annually either by venepuncture or by the capillary TSH method.[34] It is particularly important to pre-empt the development of hypothyroidism in girls receiving GH treatment.

Glucose intolerance, insulin resistance, and diabetes mellitus

Mild glucose intolerance and insulin resistance have been shown in girls receiving GH injections but these return to normal when treatment is stopped.[35] Insulin resistance has also been reported in adulthood and has implications for the development of cardiovascular disease.[36] Type 1 diabetes

mellitus is quoted as being increased in TS. However, we have found only sporadic case reports in the literature with no prevalence data. We have encountered the condition in only one of our 150 patients and do not counsel our families to be especially vigilant, suggesting that urine is checked for glucose only if polyuria and polydipsia are reported.

Ear problems

Middle ear disease, which affects 50–85% of girls and women with TS,[37] usually starts in early childhood and is a cause of significant morbidity, requiring repeated medical and surgical intervention. Problems include recurrent suppurative otitis media; otitis media with effusion (''glue ear'') resulting in conductive deafness; chronic suppurative middle ear disease with perforation; and cholesteatoma formation. The frequency of ear infections decreases with age,[38] so that by secondary school entry few girls have troublesome symptoms.

Apart from conductive hearing loss, which has been reported in 44% of a cohort of 56 TS girls, sensorineural loss is also common, affecting 58% in the same series, the youngest of whom was 6 years old.[39] Parents should be made aware of the high prevalence of ear problems at diagnosis so that they can present immediately to the family doctor if the child develops symptoms. Specific enquiry as to ear problems should be made at the paediatric clinic. Regular audiological checks should be performed with prompt referral to ENT services as required. Interventional strategies include myringotomy, insertion of ventilation tubes (''grommets''), adeno-tonsillectomy, and, with severe chronic suppurative middle ear disease, modified mastoidectomy. Some children will benefit from hearing aids, especially during school hours.

Eye problems

The most common ocular findings reported in TS are strabismus, ptosis, and amblyopia.[40 41] All patients should have an eye assessment performed, with referral to ophthalmological services as required.

Lymphoedema/foot problems

The pedal oedema with which TS may present in the newborn period usually settles in early childhood, although parents may have difficulty finding suitable shoes. Rarely, lymphoedema of the lower limbs recurs, in school age children and adolescents.[42] In troublesome cases, the wearing of a pressure stocking may be helpful. Girls with TS also display a number of structural foot problems including short broad feet, making it difficult to buy well fitting shoes, and involution of the toenails. These problems, coupled with intermittent lymphoedema, increase the risk of infection and cellulitis.[43] We recommend referral to a podiatrist for advice on foot care, nail cutting, and shoe fitting in TS girls.

Obesity

Some girls develop simple obesity during the school years. This may be related to a relatively sedentary lifestyle in some, compounded by foot problems, as previously discussed. In clinic, we try to warn parents in advance of this problem so that it can be pre-empted, and encourage sensible eating with plenty of exercise.

Neck webbing

This distressing feature results from intrauterine lymphoedema, which then regresses before birth leaving redundant neck folds. Fortunately, severe neck webbing is rare. In severe cases, surgical intervention with Z-plasty can be performed,[44] but the cosmetic result can be disappointing because of keloid formation in the scars. We therefore discourage surgery, recommending that the girl simply wears her hair long.

Behaviour patterns

Parents frequently report high activity levels,[45] reduced concentration span, poor sleeping pattern, and increased fearfulness during the preschool years. There is, unfortunately, no easy solution to this array of common childhood problems. Parents should be advised that they will settle as the child grows older, and be encouraged to adopt a firm and consistent approach to day-to-day management, including a bedtime routine. In selected cases, referral to a clinical psychologist is indicated. Early nursery school placement is often helpful.

Schooling difficulties

Intelligence is normal in most girls with TS, and mirrors that of the general population. However, schooling can be problematic for some girls with TS who may experience difficulties with number work and maths[46 47] and impaired visuospatial abilities.[48] These features, combined with a short concentration span, and conductive hearing loss can make school life very difficult. Some girls require referral for psychometric testing and educational psychology input. The teacher should be aware of any hearing problem so that the child can be appropriately seated in the classroom.

Psychosocial aspects

Although there are exceptions, TS girls tend to be more socially vulnerable than their peers. Studies have shown more internalising behaviour problems, social problems, and immaturity, and less social activity in girls with TS.[49–51] An imprinting effect has been described by Skuse *et al* who reported that girls inheriting the normal X chromosome from the father (paternal gene expression) show better social adjustment with significantly fewer educational and social difficulties, attributable to superior verbal and higher order executive function skills.[52] These aspects of TS are relevant to adult transfer.

Short stature

Short stature is almost invariable in TS, with untreated girls achieving a final height approximately 21 cm shorter than the normal female population.[53] In the UK, therefore, the mean untreated final height of women with TS is approximately 142 cm.

Growth promoting treatment

The growth promoting strategies for short stature in TS include growth hormone (GH) therapy, adjunctive therapy with the anabolic steroid oxandrolone, and low dose oestrogen therapy. Leg lengthening, although useful in other conditions such as achondroplasia, is not recommended in TS since the procedure is associated with a high incidence of postoperative complications, such as fractures, poor quality of new bone, and soft tissue problems arising from the prolonged use of external fixators.[54]

Growth hormone therapy

The primary growth promoting treatment for girls with TS is biosynthetic growth hormone, which became available in the UK in 1985, was licensed for use in TS in 1989, and was approved by the National Institute for Clinical Excellence and the Health Technology Board for Scotland in 2002. Its efficacy in improving mean final height (FH) outcome in groups of girls with TS has been established in a number of studies.[55 56] Mean FH minus projected height (so-called ''height gain'') is 5 cm or more,[57] and a target FH of 150 cm is now an achievable goal in most patients.[58 59] A recent audit of FH outcome in our own centre showed an improvement in FH of 8.5 cm over the previous Scottish figures published six years earlier: 151.1 cm versus 142.6 cm.[60] However, all studies have

shown considerable variation in individual outcome, with some individuals doing badly despite GH treatment.[55]

Age at starting treatment

Intuitively, one would expect early treatment to be associated with improved final height outcome, but a number of studies have failed to show this,[61 62] although other studies have claimed an association.[63–65] There are no data at present to show that starting treatment at a very young age (for example, 2 or 3 years) improves outcome.

We therefore counsel families to plan for starting GH when the child begins school (that is, 4–5 years), being prepared to start earlier if she is unduly short. Recent data suggest that the number of years of GH therapy prior to pubertal induction may be predictive of outcome,[63 66] and it has been suggested that a minimum of four oestrogen-free years of GH treatment should be the goal.[67] If pubertal induction is contemplated as early as 12 years, therefore, GH treatment should begin by 8 years of age.

Dose and administration

GH is usually administered as a nightly subcutaneous injection using one of a number of pen injector devices. Less often a needle-free device is used. There is evidence that an increased frequency of injections per week is associated with a better height outcome,[68] and current practice is to recommend daily GH injections.

The optimal GH dose is a matter of continuing debate. Despite reduced levels of endogenous GH secretion on stimulation testing in many individuals with TS,[69 70] no relationship between GH status and response to treatment has been shown.[71 72] It is recognised that higher doses than the 5 mg/m^2/week recommended for classic GH deficiency are required, and data from the Kabi International Growth Study (KIGS) indicate that the average dose of GH being administered to girls with TS in Europe is approximately 1.5 times the dose used to treat classical GH deficiency.[73] French and Dutch centres have shown impressive results using doses as large as 0.7 mg/kg (≈23 mg/m^2) and 0.6 mg/kg (≈18.7 mg/m^2) per week, respectively, and also incremental doses to combat waning height velocity.[74 75] However, the use of these supraphysiological doses of GH has not become current practice, possibly related to concerns over long term safety as well as the financial implications of such therapy.

In the UK, a dose of 10 mg/m^2 (≈0.3 mg/kg) per week has been adopted by the British Society for Paediatric Endocrinology and Diabetes (BSPED) in the light of pooled experience with GH in Europe.[76]

Monitoring

Clinic review 4–6 monthly is recommended in order to monitor height velocity, assess compliance, and adjust the GH dose to maintain it at 10 mg/m^2/day. IGF-I should be measured annually; this can be done using capillary blood spots.[77] This measurement can also provide a useful measure of compliance, when height velocity is disappointing.[78] Thyroid function should be monitored annually (see above). Treatment is stopped at near-FH (height velocity <2 cm per year) or when FH is reached (height velocity <1 cm per year), usually at the age of 15–16 years.

Oxandrolone therapy

The role of oxandrolone in TS remains controversial. When used in combination with GH, it has been shown to improve height velocity,[58 59] and a recent study comparing GH plus oxandrolone with GH alone has shown a mean FH of 3.4 cm greater in the combination group.[79] The impact of oxandrolone on FH is currently under investigation as part of the UK Turner Study, a randomised, double blind, placebo controlled study of growth promoting treatment in TS, organised by the BSPED. Girls receive a standard dose of GH with randomisation to oxandrolone or placebo at 9 years, and further randomisation to begin oestrogen treatment for pubertal induction at either 12 or 14 years. Over 100 participants have been enrolled at 40 UK hospitals since the study began in 1999 and final height data will be available in 2007. To date, no significant adverse effects have been reported with the doses used (see table 1).

Primary ovarian failure

All but a small proportion of girls require oestrogen treatment for pubertal induction and long term hormone replacement during adulthood.

Pubertal induction

Oral ethinyloestradiol is the most commonly used oestrogen preparation;[80 81] table 1 shows the regimen for pubertal induction used in the UK Turner Study. The optimal age at which to introduce oestrogen replacement remains contentious. Delaying induction for as long as possible has been advocated previously,[82] the rationale being to prolong the growth period before epiphyseal fusion. However, experience of recruiting for the UK Turner Study suggests that a considerable number of UK families are uncomfortable with the possible psychological consequences of late pubertal induction. Moreover, recent data from Belgium indicate that delayed puberty does not affect FH outcome.[62] Work in the US by Reiter *et al* suggests that if GH therapy is initiated early enough, puberty can be induced at an age appropriate time of 11–12 years at no detriment to final height.[63] Our most recent cohort of patients studied retrospectively reached a mean FH of 151.1 cm with pubertal induction at 12.7 years of age.[60] Until definitive evidence becomes available, we recommend starting oestrogen at 13 years, unless GH was started particularly late and/or the family has a strong preference for earlier or later induction.

Fertility, adult transfer, surveillance, and long term follow up

Fertility

While the issue of fertility is not directly applicable to TS children and adolescents, it is an important concern that needs to be properly discussed during the childhood years. Families are advised that the majority of women will require assisted conception in the form of egg donation. A small number who have some ovarian function may be able to conceive spontaneously but will require genetic counselling, in view of the increased incidence of miscarriage and congenital abnormalities.[83] Adequate uterine development is essential in either situation, with an increased risk of miscarriage if the uterus is hypoplastic.[84] The importance of complying with long term oestrogen replacement should, therefore, be emphasised. Techniques such as cryopreservation of ovarian tissue and ovarian transplantation currently remain experimental.[85] Timely referral to a reproductive specialist is recommended.

Adult transfer

TS women require surveillance to promote health, ensure adequate hormone replacement, and deal with treatable problems as set out below. There is some debate as to whether adult follow up should be supervised by the gynaecologist, endocrinologist, reproductive endocrinologist, or general practitioner. In our opinion, the exact speciality of the responsible physician is unimportant; the person needs to have a genuine interest in TS, and an ability to coordinate the multidisciplinary care required. The process of paediatric to adult handover should be carried out in an agreed, structured fashion so that the girls feel secure with their new carers. In our monthly Turner clinic, patients are seen by the

gynaecologist for a number of years before transfer to her clinic, usually around the age of 18 years.

Surveillance

This includes the early detection and treatment of hearing loss;[86] and hypothyroidism.[87] As previously discussed, women with TS also require counselling and preparation concerning assisted fertility.[84] Two particular aspects of surveillance require special mention: oestrogen replacement and cardiovascular health.

Oestrogen replacement

This is required throughout adulthood, not only to maintain uterine but also cardiac and bone health. An array of pharmaceutical preparations is available. In the general UK population, oral oestrogen replacement is standard; transdermal oestrogen usually being reserved for women with cardiovascular risk factors such as thrombosis and hypertension. In the UK TS population, HRT preparations are less popular than others, perhaps because of their cost implications and their association with menopausal women. Recent data suggest that, for reasons of peer acceptability and financial convenience, most girls are using the oral contraceptive pill (OCP).[80] However we, and others, have shown that uterine development in TS using OCPs Loestrin 20 or Loestrin 30 is sub-optimal in most individuals.[88 89] While this finding may be partly related to dysplasia inherent to TS, the fact that OCP regimens involve an oestrogen-free week, thus rendering the patient oestrogen deficient for three months in each year, may be important.

The mode of replacement may have important implications for this group of patients' reproductive health since adequate uterine development is a prerequisite for successful embryo implantation in the course of an ovum donation programme. These women are also at greater risk of developing osteoporosis and fractures,[30] making it essential that oestrogen replacement is optimised. There is a need for prospective studies examining the acceptability and efficacy of different types of oestrogen replacement, such as the BSPED's proposed UK Turner Study II, which aims to compare a commonly used OCP with a continuous oral oestrogen regimen.

At present, our preference is a regimen giving oral ethinyloestradiol 20 μg daily continuously with 5 mg of norethisterone for the first five days of each calendar month, on which regimen the girls have a monthly period.

Cardiovascular health

Women with TS have an increased risk of hypertension[90] and ischaemic heart disease.[30] Aortic root dilatation and death from aortic dissection/rupture is an increasingly recognised complication of TS.[91] Cardiac evaluation, including measurement of aortic root diameter, should be carried out at the time of adult transfer using echocardiography and MRI scanning and repeated every few years, particularly in women with a bicuspid aortic valve or those considering ovum donation.[92]

Long term follow up

The available data on follow up status of adult patients with TS are concerning. A large adult TS clinic in the UK reported that 22% of patients were receiving no oestrogen replacement of any kind at first attendance.[93] Our own experience is that many girls default from attendance at the adult clinic. In view of this, we have recently begun to invite girls to our department for a ''finishing'' session, during which we explain the condition in some detail and emphasise the benefits of adult follow up.

In an attempt to optimise the follow up of TS adults, the BSPED and Society for Endocrinology have recently collaborated to develop a National Turner Register. Patients aged 16 years and over are asked to give written informed consent to allow basic clinical details to be kept on a national register, and for the information, including contact details and follow up, to be updated annually.

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REFERENCES

1 **Nielsen J**, Wohlert M. Chromosome abnormalities found among 34,910 newborn children: results from a 13-year incidence study in Arhus, Denmark. *Hum Genet* 1991;**87**:81–3.
2 **Cockwell A**, MacKenzie M, Youings S, *et al.* A cytogenetic and molecular study of a series of 45,X fetuses and their parents. *J Med Genet* 1991;**28**:151–5.
3 **Hook EB**, Warburton D. The distribution of chromosomal genotypes associated with Turner's syndrome: livebirth prevalence rates and evidence for diminished fetal mortality and severity in genotypes associated with structural X abnormalities or mosaicism. *Hum Genet* 1983;**64**:24–7.
4 **Jacobs P**, Dalton P, James R, *et al.* Turner syndrome: a cytogenetic and molecular study. *Ann Hum Genet* 1997;**61**:471–83.
5 **Carrel L**, Cottle AA, Goglin KC, *et al.* A first-generation X-inactivation profile of the human X chromosome. *Proc Natl Acad Sci U S A* 1999;**96**:14440–4.
6 **Rao E**, Weiss B, Fukami M, *et al.* Pseudoautosomal deletions encompassing a novel homeobox gene cause growth failure in idiopathic short stature and Turner syndrome. *Nat Genet* 1997;**16**:54–63.
7 **Boucher CA**, Sargent CA, Ogata T, *et al.* Breakpoint analysis of Turner patients with partial Xp deletions: implications for the lymphoedema gene location. *J Med Genet* 2001;**38**:591–8.
8 **Ogata T**, Muroya K, Matsuo N, *et al.* Turner syndrome and Xp deletions: clinical and molecular studies in 47 patients. *J Clin Endocrinol Metab* 2001;**86**:5498–508.
9 **Zinn AR**, Tonk VS, Chen Z, *et al.* Evidence for a Turner syndrome locus or loci at Xp11.2−p22.1. *Am J Hum Genet* 1998;**63**:1757–66.
10 **Blair J**, Tolmie J, Hollman A, *et al.* Phenotype, ovarian function, and growth in patients with 45,X/47,XXX Turner mosaicism: implications for prenatal counseling and estrogen therapy at puberty. *J Pediatr* 2001;**139**:724–8.
11 **Hayward PAR**, Satsangi J, Jewell DP. Inflammatory bowel disease and the X chromosome. *Q J Med* 1996;**89**:713–18.
12 **Chiovato L**, Larizza D, Bendinelli G, *et al.* Autoimmune hypothyroidsim and hyperthyroidism in patients with Turner's syndrome. *Eur J Endocrinol* 1996;**134**:568–75.
13 **Kunsti J**, Skuse D, Elgar K, *et al.* Ring-X chromosomes: their cognitive and behavioural phenotype. *Ann Hum Genet* 2000;**64**:295–305.
14 **Collins AL**, Cockwell AE, Jacobs PA, *et al.* A comparison of the clinical and cytogenetic findings in nine patients with a ring (X) cell line and 16 45,X patients. *J Med Genet* 1994;**31**:528–33.
15 **Gravholt CH**, Fedder J, Naeraa RW, *et al.* Occurrence of gonadoblastoma in females with turner syndrome and Y chromosome material: a population study. *J Clin Endocrinol Metab* 2000;**85**:3199–202.
16 **Held KR**, Kerber S, Kaminsky E, *et al.* Hypothesis: 45,X Turner syndrome does not exist. All surviving patients have sex-chromosomal mosaicism. In: Ranke MB, Rosenfeld RG, eds. *Turner syndrome: growth promoting therapies*. Amsterdam: Elsevier Science, 1991:15–20.
17 **Turner Syndrome Support Society**. *Turner syndrome: lifelong guidance and support*. South Shields: Harlow Printing Limited, 2002.
18 **Turner Syndrome Support Society**. *Talking about Turner syndrome*. Oxford: Oxford PharmaGenesis Ltd, 2003.
19 **Stanhope R**. ed. *Turner syndrome: questions answered for parents and children*. Guildford: A&M Publishing Ltd, 2004.
20 **Stirling H**, McKane A-M. *Teens and Turner syndrome: what's it all about?* Novo Nordisk Ltd, 2003.
21 **Turner Syndrome Support Society**. *Turner syndrome and education: how to help your child survive and succeed at school*. South Shields: Harlow Printing Limited, 2004.
22 **Sybert VP**. Cardiovascular malformations and complications in Turner syndrome. *Pediatrics* 1998;**101**:e11.
23 **Gravholt CH**. Long-term follow-up of Turner syndrome. *International Growth Monitor* 2004;**14**:2–6.

24 **Nathwani NC**, Unwin R, Brook CGD, *et al*. The influence of renal and cardiovascular abnormalities on blood pressure in Turner syndrome. *Clin Endocrinol (Oxf)* 2000;**52**:371–7.
25 **Nathwani NC**, Unwin R, Brook CGD, *et al*. Blood pressure and Turner syndrome. *Clin Endocrinol (Oxf)* 2000;**52**:363–70.
26 **Lippe B**, Geffner ME, Dietrich RB, *et al*. Renal malformations in patients with Turner syndrome: imaging in 141 patients. *Pediatrics* 1988;**82**:852–6.
27 **Flynn MT**, Ekstrom L, De Arce M, *et al*. Prevalence of renal malformation in Turner syndrome. *Pediatr Nephrol* 1996;**10**:498–500.
28 **Elsheikh M**, Hodgson HJF, Wass JAH, *et al*. Hormone replacement therapy may improve hepatic function in women with Turner's syndrome. *Clin Endocrinol* 2001;**55**:227–31.
29 **Gravholt CH**. Medical problems of adult Turner's syndrome. *Horm Res* 2001;**56**:44–50.
30 **Gravholt CH**, Juul S, Naeraa RW, *et al*. Morbidity in Turner syndrome. *J Clin Epidemiol* 1998;**51**:147–58.
31 **Salerno M**, Di Maio S, Gasparini N, *et al*. Liver abnormalities in Turner syndrome. *Eur J Pediatr* 1999;**158**:618–23.
32 **Starke M**, Wikland KA, Möller A. Parents' descriptions of development and problems associated with infants with Turner syndrome: A retrospective study. *J Paediatr Child Health* 2003;**39**(4):293–8.
33 **Mathisen B**, Reilly S, Skuse D. Oral-motor dysfunction and feeding disorders of infants with Turner syndrome. *Dev Med Child Neurol* 1992;**34**:141–9.
34 **Findlay CA**, Donaldson M. How often should we screen for hypothyroidism in girls with Turner's syndrome? *Arch Dis Child* 1998;**78**:500a.
35 **Sas TCJ**, de Muinck Keizer-Schrama SMPF, Stijnen T, *et al*. Carbohydrate metabolism during long-term growth hormone (GH) Treatment and after discontinuation of GH treatment in girls with Turner syndrome participating in a randomized dose-response study. *J Clin Endocrinol Metab* 2000;**141**:769–75.
36 **Elsheikh M**, Dunger DB, Conway GS, *et al*. Turner's syndrome in adulthood. *Endocr Rev* 2002;**23**:120–40.
37 **Barrenäs M-L**, Landin-Wilhelmsen K, Hanson C. Ear and hearing in relation to genotype and growth in Turner syndrome. *Hear Res* 2000;**144**:21–8.
38 **Sculerati N**, Ledesma-Medina J, Finegold DN, *et al*. Otitis media and hearing loss in Turner syndrome. *Arch Otolaryngol Head Neck Surg* 1990;**116**:704–7.
39 **Stenberg AE**, Nylén O, Windh M, *et al*. Otological problems in children with Turner's syndrome. *Hear Res* 1998;**124**:85–90.
40 **Chrousos GA**, Ross JL, Chrousos G, *et al*. Ocular findings in Turner syndrome. *Ophthalmology* 1984;**91**:926–8.
41 **Adhikary HP**. Ocular manifestations of Turner's syndrome. *Trans Ophthalmol Soc U K* 1981;**101**:395–6.
42 **Blethen SL**, Allen DB, Graves D, *et al*. Safety of recombinant deoxyribonucleic acid-derived growth hormone: The National Cooperative Growth Study experience. *J Clin Endocrinol Metab* 1996;**81**:1704–10.
43 **Findlay CA**, Donaldson MD, Watt G. Foot problems in Turner's syndrome. *J Pediatr* 2001;**138**:775–7.
44 **Hikade KR**, Bitar GJ, Edgerton MT, *et al*. Modified Z-plasty repair of webbed neck deformity seen in Turner and Klippel-Feil syndrome. *Cleft Palate Craniofac J* 2002;**39**:261–6.
45 **Swillen A**, Fryns JP, Kleczlowska A, *et al*. Intelligence, behaviour and psychosocial development in Turner syndrome. A cross-sectional study of 50 pre-adolescent and adolescent girls [4–20 years]. *Genet Couns* 1993;**4**:7–18.
46 **Rovet J**, Szekely C, Hockenberry MN. Specific arithmetic calculation deficits in children with Turner syndrome. *J Clin Exp Neuropsychol* 1994;**16**:820–39.
47 **Mazzocco MM**. A process approach to describing mathematics difficulties in girls with Turner syndrome. *Pediatrics* 1998;**102**:492–6.
48 **Rovet JF**. The psychoeducational characteristics of children with Turner syndrome. *J Learn Disabil* 1993;**26**:333–41.
49 **Siegel PT**, Clopper R, Stabler B. The psychological consequences of Turner syndrome and review of the National Cooperative Growth Study Psychological Substudy. *Pediatrics* 1998;**102**:488–91.
50 **Boman UW**, Möller A, Albertsson-Wikland K. Psychological aspects of Turner syndrome. *J Psychosom Obstet Gynecol* 1998;**19**:1–18.
51 **McCauley E**, Feuillan P, Kushner H, *et al*. Psychosocial development in adolescents with Turner syndrome. *J Dev Behav Pediatr* 2001;**22**:360–5.
52 **Skuse DH**, James RS, Bishop DVM, *et al*. Evidence from Turner's syndrome of an imprinted X-linked locus affecting cognitive function. *Nature* 1997;**387**:705–8.
53 **Rochiccioli P**, David M, Malpuech G, *et al*. Study of final height in Turner's syndrome: ethnic and genetic influences. *Acta Paediatr* 1994;**83**:305–8.
54 **Bidwell JP**, Bennet GC, Bell MJ, *et al*. Leg lengthening for short stature in Turner's syndrome. *J Bone Joint Surg Br* 2000;**82-B**:1174–6.
55 **Guyda HJ**. Four decades of growth hormone therapy for short children: what have we achieved? *J Clin Endocrinol Metab* 1999;**84**:4307–16.
56 **Canadian Growth Hormone Advisory Committee**. Impact of growth hormone supplementation on adult height in Turner syndrome: results of the Canadian randomized controlled trial. *J Clin Endocrinol Metab* 2005;**90**:3360–6.
57 **Betts PR**, Butler GE, Donaldson MD, *et al*. A decade of growth hormone treatment in girls with Turner syndrome in the UK. *Arch Dis Child* 1999;**80**:221–5.
58 **Nilsson KO**, Albertsson-Wikland K, Alm J, *et al*. Improved final height in girls with Turner's syndrome treated with growth hormone and oxandrolone. *J Clin Endocrinol Metab* 1996;**81**:635–40.
59 **Rosenfeld RG**, Attie KM, Frane J, *et al*. Growth hormone therapy of Turner's syndrome: beneficial effect on adult height. *J Pediatr* 1998;**132**:319–24.
60 **Gault EJ**, Paterson WF, Young D, *et al*. Improved final height in Turner's syndrome following growth-promoting treatment at a single centre. *Acta Paediatr* 2003;**92**:1033–8.
61 **Rochiccioli P**, Battin J, Bertrand AM, *et al*. Final height in Turner syndrome patients treated with growth hormone. *Horm Res* 1995;**44**:172–6.
62 **Massa G**, Heinrichs C, Verlinde M, *et al*. Late or delayed induced or spontaneous puberty in girls with Turner syndrome treated with growth hormone does not affect final height. *J Clin Endocrinol Metab* 2003;**88**:4168–74.
63 **Reiter EO**, Blethen SL, Baptista J, *et al*. Early initiation of growth hormone treatment allows age-appropriate estrogen use in Turner's syndrome. *J Clin Endocrinol Metab* 2001;**86**:1936–41.
64 **Quigley CA**, Crowe BJ, Anglin DG, *et al*. Growth hormone and low dose estrogen in Turner syndrome: results of a United States multi-centre trial to near-final height. *J Clin Endocrinol Metab* 2002;**87**:2033–41.
65 **Ranke MB**, Partsch CJ, Lindberg A, *et al*. Adult height after GH therapy in 188 Ullrich-Turner syndrome patients: results of the German IGLU Follow-Up Study 2001. *Eur J Endocrinol* 2002;**147**:625–33.
66 **Chernausek SD**, Attie KM. Role of oestrogen therapy in the management of short stature in Turner syndrome. *Acta Paediatr Suppl* 1999;**433**:130–2.
67 **Price DA**, Ranke MB. Growth hormone in Turner syndrome. *Arch Dis Child* 2001;**84**:531.
68 **Ranke MB**, Lindberg A, Chatelain P, *et al*. Turner syndrome: demography, auxology and growth during growth hormone therapy in KIGS. In: Ranke MB, Wilton P, eds. *Growth hormone therapy in KIGS—10 years experience*. Heidelberg: Johann Ambrosius Barth Verlag, 1999:245–58.
69 **Albertsson-Wikland K**, Rosberg S. Pattern of spontaneous growth hormone secretion in Turner syndrome. In: Ranke MB, Rosenfeld RG, eds. *Turner syndrome: growth promoting therapies*. Amsterdam: Elsevier Science, 1991:23–8.
70 **Pirazzoli P**, Mazzanti L, Bergamaschi R, *et al*. Reduced spontaneous growth hormone secretion in patients with Turner's syndrome. *Acta Paediatr* 1999;**88**:610–13.
71 **Tanaka T**, Hibi I, Shizume K, *et al*. GH secretion capacity in Turner syndrome and its influence on the effect of GH treatment. In: Ranke MB, Rosenfeld RG, eds. *Turner syndrome: growth promoting therapies*. Amsterdam: Elsevier Science, 1991:41–5.
72 **Cavallo L**, Gurrado R. Endogenous growth hormone secretion does not correlate with growth in patients with Turner's syndrome. *J Pediatr Endocrinol Metab* 1999;**12**:623–7.
73 **Ranke MB**, Lindberg A, Chatelain P, *et al*. Prediction of long-term response to recombinant human growth hormone in Turner syndrome: development and validation of mathematical models. *J Clin Endocrinol Metab* 2000;**85**:4212–18.
74 **Carel J-C**, Mathivon L, Gendrel C, *et al*. Near normalization of final height with adapted doses of growth hormone in Turner's syndrome. *J Clin Endocrinol Metab* 1998;**83**:1462–6.
75 **van Pareren YK**, de Muinck Keizer-Schrama S, Stijnen T, *et al*. Final height in girls with Turner syndrome after long-term growth hormone treatment in three dosages and low dose estrogens. *J Clin Endocrinol Metab* 2003;**88**:1119–25.
76 **Donaldson MD**. Growth hormone therapy in Turner syndrome—current uncertainties and future strategies. *Horm Res* 1997;**48**:35–44.
77 **Das U**, Whatmore AJ, Khosravi J, *et al*. IGF-I and IGF-binding protein-3 measurements on filter paper blood spots in children and adolescents on GH treatment: use in monitoring and as markers of growth performance. *Eur J Endocrinol* 2003;**149**:179–85.
78 **Tillmann V**, Patel L, Gill MS, *et al*. Monitoring serum insulin-like growth factor-I (IGF-I), IGF binding protein-3 (IGFBP-3), IGF-I/IGFBP-3 molar ratio and leptin during growth hormone treatment for disordered growth. *Clin Endocrinol* 2000;**53**:329–36.
79 **Stahnke N**, Keller E, Landy H, *et al*. Favourable final height outcome in girls with Ullrich-Turner syndrome treated with low-dose growth hormone together with oxandrolone despite starting treatment after 10 years of age. *J Pediatr Endocrinol Metab* 2002;**15**:129–38.
80 **Bath LE**, Critchley HOD, Kelnar CJH, *et al*. Choice of hormone replacement therapy in young women with ovarian failure. *Clin Endocrinol* 2001;**55**:697–8.
81 **Kiess W**, Conway G, Ritzen M, *et al*. Induction of puberty in the hypogonadal girl—practices and attitudes of pediatric endocrinologists in Europe. *Horm Res* 2002;**57**:66–71.
82 **Cacciari E**, Mazzanti L, Italian Study Group for Turner Syndrome. Final height of patients with Turner's syndrome treated with growth hormone (GH): indications for GH therapy alone at high doses and late estrogen therapy. *J Clin Endocrinol Metab* 1999;**84**:4510–15.
83 **Tarani L**, Lampariello S, Raguso G, *et al*. Pregnancy in patients with Turner's syndrome: six new cases and review of literature. *Gynecol Endocrinol* 1998;**12**:83–7.
84 **Khastgir G**, Abdalla H, Thomas A, *et al*. Oocyte donation in Turner's syndrome: an analysis of the factors affecting the outcome. *Hum Reprod* 1997;**12**:279–85.
85 **Hovatta O**. Methods for cryopreservation of human ovarian tissue. *Reprod Biomed Online* 2005;**10**:729–34.
86 **Beckman A**, Conway GS, Cadge B. Audiological features of Turner's syndrome in adults. *Int J Audiol* 2004;**43**:533–44.
87 **El Mansoury M**, Bryman I, Berntorp K, *et al*. Hypothyroidism is common in Turner syndrome: results of a five-year follow-up. *J Clin Endocrinol Metab* 2005;**90**:2131–5.
88 **Paterson WF**, Hollman AS, Donaldson MDC. Poor uterine development in Turner syndrome with oral oestrogen therapy. *Clin Endocrinol* 2002;**56**:359–65.

89 **Snajderova M**, Mardesic T, Lebl J, *et al*. The uterine length in women with Turner syndrome reflects the postmenarcheal daily estrogen dose. *Horm Res* 2003;**60**:198–204.
90 **Elsheikh M**, Casadei B, Conway GS, *et al*. Hypertension is a major risk factor for aortic root dilatation in women with Turner's syndrome. *Clin Endocrinol* 2001;**54**:69–73.
91 **Lin AE**, Lippe B, Rosenfeld RG. Further delineation of aortic dilation, dissection and rupture in patients with Turner syndrome. *Pediatrics* 1998;**102**:e12.
92 **Ostberg JE**, Brookes JAS, McCarthy C, *et al*. A comparison of echocardiography and magnetic resonance imaging in cardiovascular screening of adults with Turner syndrome. *J Clin Endocrinol Metab* 2004;**89**:5966–71.
93 **Conway GS**, Elsheikh M, Cadge B, *et al*. Adult Turner follow-up—the Middlesex experience. In: Saenger P, Pasquino AM, eds. *Optimizing health care for Turner patients in the 21st century*. Amsterdam: Elsevier Science, 2000:295–306.

IMAGES IN PAEDIATRICS

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Congenital subependymal giant cell astrocytoma diagnosed on fetal MRI

A primiparous mother had an antenatal ultrasound at 21 weeks' gestation, which showed a mass in the left side of the brain arising from the intraventricular region and several cardiac tumours, most likely to be rhabdomyomas. An MRI scan at 24 weeks' gestation showed an intraventricular mass in the fronto-parietal part of the left cerebral hemisphere of the fetus (fig 1). The lesion was of high signal on T1 weighted sequence and low on T2. The boy was born at 36 weeks' gestation. Physical and neurological examination was normal. Postnatal cranial ultrasound and MRI confirmed a large mass lesion involving the left lateral ventricle; within the body of the right ventricle was a solitary subependymal nodule (fig 2). Based on the radiological abnormalities of the brain and heart, tuberous sclerosis (TS) was strongly suspected. The tumour in the left hemisphere fulfilled the neuroradiological diagnostic criteria for a subependymal giant cell astrocytoma (SEGA).[1] There was no history or evidence of TS on clinical examination of family members. Genetic testing of the neonate showed the mutation for TS.

At 2 months he developed right focal seizures and anticonvulsant therapy was commenced. EEG showed hypsarrhythmia. At 10 months of age he underwent surgical excision of the brain tumour, confirmed histologically as a SEGA. Now aged 1 year, his development is within normal limits and his seizures are controlled.

SEGAs are rare brain tumours that occur typically in the walls of the lateral ventricles and are generally located near the foramen of Monro. They are nearly always associated with TS.[2 3] They are usually discovered in the second decade of life and only rarely occur in infancy.[4] To our knowledge this the first report of a SEGA diagnosed on fetal MRI. Although they are benign in nature and grow slowly, they represent a major cause of death due to raised intracranial pressure or haemorrhage in patients with TS.[5]

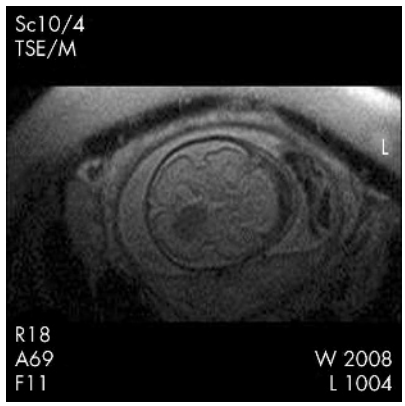

Figure 1 Fetal MRI scan. Axial T2 weighted image at 24 weeks, showing a low signal mass in the body of the left lateral ventricle.

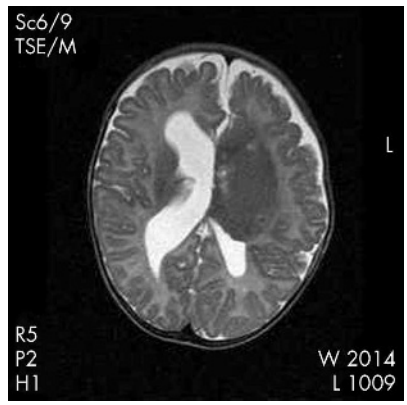

Figure 2 Postnatal MRI scan. Axial T2 weighted sequence, showing large mass lesion involving the body and frontal horn of the left lateral ventricle. Within the body of the right ventricle was a solitary subependymal nodule.

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References

1 **Griffiths PD**, Martland TR. Tuberous sclerosis complex: the role of neuroradiology. *Neuropediatrics* 1997;**28**:244–52.
2 **Haslam RHA**. Tuberous sclerosis. In: Buyse ML, ed. *Birth defects encyclopedia*. Cambridge, MA: Blackwell, 1990:1712–14.
3 **Reznik M**, Pierard GE. Neurophakomatoses and allied disorders. In: Duckett S, ed. *Pediatric neuropathology*. Malvern, PA: Williams & Wilkins, 1995:740–3.
4 **Shepherd CW**, Scheithauer B, Gomez MR. Brain tumors in tuberous sclerosis: a clinicopathologic study of the mayo clinic experience. *Mayo Clin Proc* 1991;**66**:378–9.
5 **Gomez MR**. The phakomatoses. In: Gomez MR, ed. *Tuberous sclerosis*. New York: Raven Press, 1998:16–20.