



Tuberous Sclerosis Complex (often referred to as TSC or TS) is a common multi-system disorder affecting 1:5,000 to 1:10,000 newborns and is caused by damage to one of two genes which regulate cell growth. It results in hamartomas or tumours which can affect a variety of organs, most commonly the brain, skin and kidneys. It can present at any age from antenatally to adulthood, with considerable variation in severity. The disease results from a mutation of either the TSC1 gene on chromosome 9 or the TSC2 gene on chromosome 16. The condition is transmitted as an autosomal dominant trait but 60-70% of cases are sporadic and represent new mutations.

This is a short summary of the Clinical Guidelines, which are available on request from tuberous-sclerosis.org. These should be consulted for further detailed information and to establish an integrated pathway of care for the patient. These are guidelines only and are not meant to be prescriptive.

Evidence for the recommendations is graded as follows:

- A: Randomised controlled trials backed by a good body of literature
- B: As A but with well-conducted clinical studies instead of randomised controlled trials
- C: Evidence from expert committees or clinicians

Initial diagnosis

The complete Clinical Guidelines should be consulted for the full recommended investigations based on the diagnostic criteria (see Appendix 1).

Recommendations for initial diagnosis (B)

- Take personal and family history
- Perform clinical examination, to include fundoscopy and examination of skin with UV light
- Cranial imaging e.g. MRI scan or non enhanced CT
- Renal ultrasound
- Echocardiography in infants
- Ensure diagnostic criteria (Appendix 1) are satisfied

Family screening and genetic counselling

Any child of a person diagnosed as having TSC has up to a 50% chance of inheriting the disease. Family screening and genetic counselling should be carried out by referral to a clinical genetics service. The purpose is firstly, to discover if other family members have TSC and secondly, to quantify the risks for the parents and other family members of having children with TSC. DNA testing is available in 85% of cases and should be discussed. Germline mosaicism (previously called gonadal mosaicism) is possible and means that where parents do not appear to have TSC elsewhere, only the ovaries or testes may be affected, so that 2% will have children with TSC.

Recommendations for family screening (B)

- Investigate family members when indicated, including family history
- Clinical examination including examination of skin with UV light and fundoscopy
- Brain CT or MRI
- The offer of genetic counselling

Evaluation and monitoring - clinical problems

Evaluation should be annual or more frequent if needed. History and examination should ascertain whether current problems are under control or new ones occurred.

Recommendations for evaluation and monitoring (C)

The primary physician should investigate whether there are any problems that need attention, both at diagnosis and each follow-up visit, relating to:

- Epilepsy
- Neurological problems
- Cardiac symptoms
- Skin lesions
- Kidney complications
- Pulmonary problems
- Developmental and psychological problems

Epilepsy

Seizures occur in 65% of patients with TSC, often presenting in infancy with infantile spasms. Control can be difficult and 85% of children who develop seizures still have them by the age of 5 years. Seizures, especially infantile spasms in the early years of life, may result in learning disability, so early diagnosis and control are paramount.

Complete remission of fits is less common with TSC than with idiopathic epilepsy. If seizures continue, referral to a specialist epilepsy clinic will be appropriate. Special care must be taken with anti-epileptic drugs that may exacerbate some of the behaviour problems associated with TSC. Vigabatrin may cause visual field defects although current evidence strongly suggests the benefits of its use in children with infantile spasms, or epilepsy uncontrolled by other means, outweigh the risks. Special monitoring of visual fields is recommended. A diagnosis of TSC or the presence of multiple cortical tubers does not preclude epilepsy surgery. An EEG is necessary for patients having seizures to try to clarify the seizure disorder. Some form of EEG may also be useful in any new or unexplained behaviour problems, including sleep disturbance and sudden onset brief apparent mood depression. The possibility of partial seizures or non-convulsive status should be considered in these cases. Patients should have access to 24 hour EEG and video EEG when necessary.

Recommendations for epilepsy (B)

- Review current seizures
- Review current anti-epileptic medication
- Perform EEG if applicable

Neurological problems

A sub-ependymal giant cell astrocytoma (SEGA) occurs in 5% -15% of patients with TSC. This normally manifests in late childhood or early teenage years, with neurological problems due to hydrocephalus. Suggestive signs or symptoms include headache, vomiting, focal neurological signs e.g. visual deterioration,

new squint, limp, difficulty in walking, deterioration in intellectual function, unexplained deterioration in fits and head banging or other behaviour suggestive of severe headache. These require urgent investigation with neuroimaging. MRI is preferred to CT because of the risk from ionizing radiation but urgency is paramount. Children should be referred to a recognised paediatric neurology centre. The standard treatment was surgical excision. The less advanced the lesion the better the results. SEGAs behave as benign tumours but may recur locally if excision is incomplete. Everolimus (Votubia®) is an mTOR inhibitor that has now been shown to shrink SEGAs and is licensed for use.

An enlarging lesion, or one greater than 12mm diameter, is more likely to be a SEGA than a SEN. Calcified subependymal nodules (SEN) are best seen on a non-enhanced CT. They are found in 80% of affected individuals. MRI scanning is more sensitive, picking up cortical tubers and cortical lesions, although the latter are not necessarily specific to TSC. A normal CT or the absence of cortical tubers on MRI does not exclude the diagnosis of TSC. Brain imaging is needed in every case where there are neurological complications. MRI is best because it demonstrates a better range of pathology and is useful for planning future surgery (if indicated). It also does not result in a radiation dose. If the MRI is normal or diagnosis still uncertain, a CT should be performed.

Recommendation for neurological problems (C)

For new and unexplained behaviour problems, mood changes, sleep disturbance or non-convulsive status:

- Perform urgent brain scan (MRI preferred to CT) if symptoms/signs suggest raised intracranial pressure or there are focal neurological symptoms or signs

Cardiac Problems

Cardiac rhabdomyomas are common in neonates but rarely cause medical complications. Arrhythmia can occur, most commonly Wolff-Parkinson-White syndrome. Spontaneous improvement often occurs, perhaps because the lesions that cause it rapidly decrease in size after birth. Arterial aneurysms can also occur.

Recommendation for cardiac evaluation (C)

- ECG if symptoms of arrhythmia or pre- operatively or in cases of unexplained loss of consciousness

Skin lesions

Facial angiofibromas usually develop in childhood but can appear for the first time in adults. The rash normally becomes progressively more florid until early adulthood but may continue to deteriorate through adult years. The lesions are papular and either red or flesh coloured depending upon the proportions of vascular and fibrous tissue contained. Laser therapy frequently results in a marked improvement, especially in vascular lesions. Argon lasers and pulsed dye lasers are best for the red vascular lesions and CO2 lasers for the more fibrous type.

Multiple unsightly skin tags can be removed with cryotherapy. Ungual fibromas can be removed by diathermy, cryotherapy, CO2 laser or surgery as needed, but tend to recur unless the area of nail bed from which they arise is destroyed.

Fibrous plaques on the forehead and shagreen patches have been treated with both laser therapy and plastic surgery. They only need intervention when they are obvious and distressing for the patient.

Recommendation for skin lesions (B)

- Consider treatment of facial angiofibromas and other skin lesions

Renal complications

In TSC there are 3 main renal complications:

1. Renal angiomyolipoma (AML): Renal AMLs are benign hamartomas containing smooth muscle cells, blood vessels and fat. They are present in 80% of people with TSC. They can be detected radiologically in early childhood when they are usually asymptomatic. Symptoms from single or multiple AMLs usually occur in adults. The main complications of AMLs are intraperitoneal or intrarenal/ureteric haemorrhage which can present as abdominal pain, haematuria or, in cases of large bleeds, as hypovolaemic shock. If lesions grow very large they can cause mechanical problems or occasionally renal failure due to replacement of the normal renal tissue. This is not common and most patients with bilateral AMLs have normal renal function. Most AMLs that have bled are found to be greater than 3cm in diameter and still enlarging. The first line treatment for a bleeding AML is percutaneous arterial embolisation, with the second choice being conservative renal sparing surgery. Extensive or repeated surgery can frequently cause renal impairment. All attempts should be made to avoid a nephrectomy. It is important to distinguish an expanding AML from a renal cell carcinoma. Usually the high fat content of the AML will allow it to be easily distinguished using ultrasound, CT or MRI. Difficulties arise in trying to distinguish a renal cell carcinoma from an AML with low fat content. Percutaneous needle biopsy may be useful in distinguishing the two lesions; AMLs avidly take up the stain for HMB45. mTOR Inhibitors have now been shown to shrink AMLs. Everolimus is undergoing Phase 3 trials to assess its place in prophylactically preventing bleeding. Many specialist TSC clinics currently prophylactically embolise AMLs which are greater than 3cm and still growing.

2. Polycystic kidney disease (PKD): Single or multiple simple cysts occur in 20% of people with TSC, have no clinical significance and can disappear over time. Polycystic kidney disease occurs in fewer than 5% of people and may cause hypertension and end stage renal failure, often in children as well as adults. Renal function should be assessed regularly in children and adults with PKD.

3. Renal cell carcinoma: Renal cell carcinoma occurs in less than 1% of patients with TSC. It often occurs at a younger age than sporadic renal cell carcinoma, in either sex and may be bilateral, is slow growing and slow to metastasize. Treatment is by complete surgical excision. Care is needed to distinguish a tumour from an AML with low fat content. As renal cell carcinomas are rare a solid lesion on imaging with a low fat content is more likely to be an AML.

Recommendations for monitoring of renal disease (B)

- Measure blood pressure annually
- Test renal function (e.g. U&E and plasma creatinine) regularly in adults and children with PKD
- Test renal function if indicated when AMLs present
- Perform renal ultrasound and repeat annually, if known lesion, or if indicated
- Refer to specialist clinic if visible haematuria occurs
- Refer to specialist clinic if treatment of renal lesion contemplated
- Solid renal lesions with a low fat content on ultrasound should be carefully investigated by an expert
- Consider prophylactic treatment of AMLs greater than 3cm that are still growing (recommendation grade C)

Pulmonary complications

Symptomatic pulmonary lymphangiomyomatosis is a rare (5%) condition that occurs almost exclusively in female patients with TSC. It usually presents in adulthood but can present earlier. It can cause progressive respiratory impairment associated with emphysematous changes and loss of lung volume. High resolution CT may be needed to confirm the diagnosis. It may be complicated by pneumothoraces and is very variable in severity. Patients undergoing positive pressure ventilation (for instance, during anaesthesia) or air travel are at risk of pneumothoraces. Some minor degree of lung involvement is present in up to 50% of women with TSC; however it rarely causes symptoms.

Recommendations for pulmonary problems (B)

If symptomatic, perform respiratory investigations, including:

- Spirometry
- Chest xray
- High resolution CT

Developmental disorders and intellectual impairment

General delay in development (intellectual impairment) occurs in between 40-60% of individuals with TSC as do specific developmental disorders such as language, reading/spelling and motor disorders. The likelihood of intellectual impairment is greatest in children who present with infantile spasms. Epilepsy control may be relevant to the development of attention difficulties. The presence of developmental and learning problems increases the likelihood of associated behavioural and psychiatric disturbance. Early identification of problems and the provision of the appropriate remedial help is important in order to ensure optimum fostering of the child's skills. A statement of special educational need may be required to ensure adequate resources to meet the child's needs.

People with intellectual impairment retain their capacity to learn well into their 30's and 40's, so educational opportunities should continue after school age ends.

Recommendations for developmental assessment (C)

- If developmental delay is suspected, assess intellectual and cognitive profile at key stages in order to identify problems early and act accordingly (age 2-3 and 7-8 years)
- Access specialist services for children and adults with intellectual impairment and neuropsychological impairments, as required
- Assess need for support from community Learning Disabilities Team

Psychological problems

Intellectual impairment frequently occurs in conjunction with behavioural problems, but this need not always be so. Psychiatric and behavioural problems are amongst the most common difficulties found in association with TSC and often families find these disorders the most demanding of their resources.

Autism is reported in around 25% of cases and more broadly defined pervasive developmental disorders occur in approximately 50%. Disruptive behaviour disorders characterised by marked hyperactivity and/or attention deficits occur in 50-60%.

Sleep disturbances are very common and more likely if the child's epilepsy is poorly controlled. Other behaviour problems: e.g. aggression, rage attacks and self-injury arise in a substantial minority of children.

The treatment and management of the disturbances requires well co-ordinated multidisciplinary services. Current evidence and theoretical considerations suggest that standard treatments including pharmacological and psychotherapeutic interventions with appropriate modifications to take account of the nature of the disease, can be effective. Prompt identification and early treatment of any associated psychopathology has widespread benefits for the child and their family.

Recommendations for psychiatric and behavioural disturbances (C)

- Investigate for pervasive developmental disorders at age 2 years e.g. CHAT test and again at school entry aged 4-5 years. e.g. ADIQ test, if developmental delay suspected

Screening for psychiatric and behavioural disturbances is required:

- At school entry
- Again at 7 years
- At secondary school transition
- During mid-adolescence (age 15 years)
- Refer to specialist mental health services if required

Social Aspects

Recommendations for social care (C)

- Consider social help (consider disability living allowance)
- Consider full needs assessment
- Consider social placement
- Ensure awareness of Tuberous Sclerosis Association support group

Appendix 1

Revised diagnostic criteria for Tuberous Sclerosis Complex (Modified from Gomez, M R: Tuberous Sclerosis Complex - 3rd Edition). A definitive diagnosis of TSC requires 2 major features. Cerebral MRI or non-enhanced CT, renal ultrasound or cardiac echo may be necessary to arrive at this. Where doubt exists or TSC is suspected but not proven, refer to a specialist centre.

Diagnostic Criteria for TSC

Major Features	Location	Timeline
Facial angiofibromas or forehead plaque	head	childhood - adulthood
Nontraumatic ungual or periungual fibroma	fingers/toes	adolescence – adulthood
Hypomelanotic macules (3 or more)	skin	from infancy
Shagreen path (connective tissue nevus)	skin	from childhood
Cortical tuber (a)	brain	from foetus
Multiple retinal nodular hamartomas	eyes	from infancy
Subependymal nodule (SEN)	brain	childhood – adulthood
Subependymal giant cell astrocytoma (SEGA)	brain	childhood – adulthood
Cardiac rhabdomyoma, single or multiple (e)	heart	from foetus – childhood
Pulmonary lymphangiomyomatosis (LAM) (b) and /or Renal angiomyolipoma (AML) (b)	lungs kidneys	adolescence – adulthood childhood – adulthood
A pathogenic mutation in TSC1 or TSC2 on gene analysis		

Suggestive features requiring further investigation

Multiple, randomly distributed pits in dental enamel teeth		
Hamartomatous rectal polyps (c)	rectum	
Bone cysts (d)	bones	
Cerebral white matter radial migration lines (a,d)	brain	
Gingival fibromas	gums	
Nonrenal hamartoma (c)	liver, spleen, other organs	
Retinal achromic patch	eyes	
“Confetti” skin lesions	skin	
Multiple renal cysts (c)	kidneys	
Skin tags	skin	
Positive family history in first degree relative		

Notes:

- (a) When cerebral cortical dysplasia and cerebral white matter radial migration lines occur together, they should be considered as one rather than two features of TSC
- (b) When both lymphangiomyomatosis and renal angiomyolipomas are present together, other features of TSC must be identified before a definite diagnosis is assigned
- (c) Histological confirmation of these features is suggested
- (d) Radiographic confirmation of these features is sufficient
- (e) On echo in child or at post mortem

This summary is adapted from Guidelines compiled by the Professional Advisers of the Tuberous Sclerosis Association based on published clinical evidence.

Revised by Dr Chris Kingswood September 2011

Further information on TSC and the work of the Tuberous Sclerosis Association can be obtained from our website at: www.tuberous-sclerosis.org

While every effort is made to ensure that our publications are correct, please note that some information may change after the date of printing. Information in this leaflet is not intended to be a substitute for medical advice from your own doctors, who know your individual circumstances. We strongly recommend you talk to your doctor, and share the above information. The TSA cannot be held responsible for any actions taken as a result of using TSA information resources.

Registered Charity No.1039549 A Company Limited by Guarantee Registered in England No. 2900107