Information sheet for health professionals helping families of a child newly diagnosed with Tuberous Sclerosis Complex (TSC)

Tuberous Sclerosis Australia

This information will help you support families who have a child who has been diagnosed with TSC. It will also help you provide care for a child where TSC is suspected.

This information sheet is not intended to be given to families. Tuberous Sclerosis Australia (TSA) publishes information resources specifically written for families of children diagnosed with TSC. TSA also publishes separate health professional and family information for a prenatal diagnosis of tuberous sclerosis. Please obtain printed copies from TSA or download the materials for families to help you explain this complex disease to them from parachute.tsa.org.au

What is TSC?

TSC is a rare disease, but it is not as rare as you may think, with an incidence of 1 in 6,000 or a prevalence of 8.8 in 100,000 births[1,2]. TSC is a genetic disease associated with variable neurodevelopmental outcomes, autism, epilepsy and benign tumours in various organs (heart, skin, brain, kidneys and lungs).

What causes TSC?

TSC is an autosomal dominant condition. People with TSC have a heterozygous mutation in either the *TSC1* or *TSC2* genes. In ⅔ of cases, it is caused by a *de novo* mutation and is not inherited from either parent. In ⅓ of cases, it is inherited from an affected parent. Some parents are so mildly affected they are unaware that they have TSC.

Major features [5]	Minor features [5]
Hypomelanotic macules (≥3, at least 5mm)	'Confetti' skin lesions
Angiofibromas (≥3) or fibrous cephalic plaque	Dental enamel pits (>3)
Ungual fibromas (≥2)	Intraoral fibromas ≥2
Shagreen patch	Retinal achromic patch
Multiple retinal hamartomas	Multiple renal cysts
Cortical tubers and/or radial migration lines	Non-renal hamartomas
Subependymal nodule (SEN) (≥2)	Sclerotic bone lesions
Subependymal giant cell astrocytoma (SEGA)	
Cardiac rhabdomyomas	
Lymphangioleiomyomatosis (LAM)	
Angiomyolipoma (renal AML) (≥2)	

What is the prognosis?

TSC is a highly variable condition. Some people will have significant disabilities caused by TSC, but many will have an IQ in the normal range. New treatment approaches and earlier interventions mean that a baby born today is likely to have a good quality of life.

mTOR inhibitors are approved treatments for TSC related subependymal giant cell astrocytoma (SEGA), renal angiomyolipoma (AML)s and focal epilepsy. Off-label topical treatment with a compounded mTOR inhibitor is also widely used for facial angiofibromas.

Early epilepsy treatment in young children has the potential to reduce rates of intractable epilepsy and improve developmental outcomes. Abnormal electrical activity can be seen on EEG before the development of clinical seizures. Clinical trials suggest that early diagnosis and close monitoring through regular EEG are both important to maximise developmental outcomes. Early treatment with the anticonvulsant vigabatrin may also play a role.

How is TSC diagnosed?

TSC is most commonly diagnosed by clinical symptoms. Imaging, such as brain MRI and renal ultrasound, is recommended to actively look for features of TSC as most are asymptomatic. A definite diagnosis of TSC requires the presence of 2 major diagnostic criteria, or 1 major with ≥ 2 minor features[5]. A possible diagnosis of TSC requires only 1 major feature or ≥ 2 minor features. A possible diagnosis may be confirmed through genetic testing if a pathogenic mutation in *TSC1* or *TSC2* is found. A pathogenic mutation is usually found in 80-90% of cases of TSC[3].

Recommendations

1. Infants with one or more cardiac rhabdomyomas should be assessed for the possibility of TSC, including a brain MRI and a renal ultrasound to look for features associated with TSC.
2. Children with a possible or definite diagnosis of TSC should be reviewed by a physician with expertise in TSC, so that accurate genetic counselling can be provided. Contact TSA for assistance with referrals.
3. Children with TSC under 2 years of age who have not developed seizures should be actively monitored for signs of seizures, including regular EEG monitoring to look for early electrical signs.

This is a publication of Tuberous Sclerosis Australia (TSA), written in collaboration with Dr Clara Chung, Clinical Geneticist, Sydney Children's Hospital. Publication was made possible thanks to the financial support of nib foundation.

This information is endorsed by Dr Kate Riney, Paediatric Neurologist & Epileptologist and Lead Clinician, TSC Clinic, Queensland Children's Hospital, Brisbane; Dr John Lawson, Paediatric Neurologist and TSC Clinic Co-director, Sydney Children's Hospital and Dr David Mowat, Clinical Geneticist and TSC Clinic Co-director, Sydney Children's Hospital.

nib foundation

Signs and symptoms of TSC	Recommendations for children newly diagnosed with TSC [5]
Genetics An affected individual has a 1 in 2 chance of having a child with TSC. If TSC resulted from a *de novo* mutation, the chance of recurrence in a sibling is very low.	Review the newly diagnosed individual's nearest three generations (siblings, parents and grandparents). Genetic testing or family counselling when TSC diagnosis is in question should be offered.
Brain The benign tumours associated with TSC include cortical tubers and subendymal nodules (SENs). Subependymal giant cell astrocytomas (SEGAs) can develop and grow. Approximately 80-90% of patients will develop seizures.	Undergo MRI of the brain to look for possible tubers, subependymal nodules (SENs) and subependymal giant cell astrocytomas (SEGAs). Obtain a baseline routine EEG; if EEG is abnormal, and particularly if features of TAND (see below) are present, try to follow this with 24-hour video EEG to look for subtle seizure activity. Refer the patient to a neurologist with experience in epilepsy associated with TSC. **For children aged under 3:** Teach parents and other caregivers of children under 3 years of age about how to recognize focal seizures and infantile spasms and what to do if they suspect the child is having seizures. More information and links to videos are available at parachute.tsa.org.au
TSC Associated Neuropsychiatric Disorders (TAND) There will be some degree of developmental disability (including autism) in 50-60% of cases. Neurodevelopmental outcome is linked to the age of seizure onset and seizure severity. Early recognition and treatment of seizures with anticonvulsants such as vigabatrin has the potential to reduce the severity of epilepsy and may, in turn, improve developmental outcome. Emerging literature also suggests that mTOR inhibitors may improve seizure and developmental outcomes. The benefit of preventative use of vigabatrin is currently being researched. It is expected that a baby born today with TSC will have better neurodevelopmental outcomes than in previous generations.	Look for signs of TAND using the TAND checklist available from tsa.org.au/TAND This is a validated screening tool for the interrelated behavioural, intellectual, and neuropsychiatric features common in TSC, designed to be used by clinicians. Family members, parents or other caregivers may also need psychological and social support.
Skin Almost all individuals with TSC will have some signs of TSC on their skin. Hypopigmented macules usually develop from a few months of age. In later childhood, other skin manifestations can develop, including angiofibromas. Topical mTOR inhibitors can be used to reduce the size of angiofibromas.	Undergo dermatological and dental examinations to check for abnormalities of the skin and teeth that are frequently associated with TSC.
Heart At least 50% of children with TSC have cardiac rhabdomyomas. Cardiac rhabdomyomas are most commonly found in the ventricles but some are situated in the atria or on the valves. They can increase in size during pregnancy. They usually do not cause symptoms and usually regress postnatally. Large lesions can lead to haemodynamic compromise by obstructing bloodflow or lead to arrhythmia.	Obtain a routine electrocardiogram (ECG) to check for abnormal heart rhythm. Obtain an echocardiogram to assess cardiac function and presence of rhabdomyomas (especially in children under 3 years of age).
Kidneys Although angiomyolipomas (AMLs) and cysts can develop and grow, they usually develop in later childhood. A small proportion of patients have a contiguous deletion of the *TSC2* and *PKD1* genes, resulting in polycystic kidney disease. Renal impairment and hypertension may develop if AMLs are large.	MRI of the abdomen is preferred to check for possible renal angiomyolipomas or cysts. Currently in Australia, an ultrasound/imaging of the kidneys is much more commonly used in place of an MRI of the abdomen. Kidney function (glomerular filtration rate, or GFR) and blood pressure should be measured.
Eyes Hamartomas can develop in the retina but do not usually affect vision.	Undergo an exam by an ophthalmologist for possible vision problems or abnormalities of the retina.
Teeth Issues such as dental enamel pits may develop.	Undergo a detailed examination by a dentist.
Lungs During adulthood, lymphangioleiomyomatosis (LAM) can develop in approximately 30% of females with TSC. Males rarely develop LAM. LAM may not cause any symptoms but may lead to shortness of breath and reduced lung function.	Tests for LAM are only required for adult females. Younger females and adult males should only be evaluated for LAM when clinical symptoms are present that heighten suspicion (such as unexplained chronic cough, chest pain, or breathing difficulties).

This information sheet is available at tsa.org.au/health-professional

Next steps

- TSA offers a range of information and support services to families living with TSC. TSA also maintains a list of health professionals with expertise in TSC.
- Regular, lifelong surveillance is recommended, including imaging of the brain and kidneys.
- Visit tsa.org.au for information about TSC health professionals and a checklist of ongoing surveillance.
- To contact TSA please email info@tsa.org.au or phone 1300 733 435 (Australia only).

References

1. O'Callaghan FJ, Shiell AW, Osborne JP, Martyn CN. Prevalence of tuberous sclerosis estimated by capture-recapture analysis. Lancet. 1998;351(9114). doi:10.1016/S01406736(05)78872-3.
2. Osborne JP, Fryer A, Webb D. Epidemiology of Tuberous Sclerosis. Ann N Y Acad Sci. 1991;615(1):125-127. doi:10.1111/j.1749-6632.1991.tb37754.x.
3. Northrup H, Krueger DA. Tuberous Sclerosis Complex Diagnostic Criteria Update: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol. 2013;49(4):243-254. doi:10.1016/j.pediatrneurol.2013.08.001.
4. Krueger DA, Northrup H, Northrup H, et al. Tuberous Sclerosis Complex Surveillance and Management: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol. 2013;49(4):255-265. doi:10.1016/j.pediatrneurol.2013.08.002.
5. Northrup H, Aronow ME, Bebin EM, Rowbin AJ, Krueger DA. Updated International Tuberous Sclerosis Complex Diagnostic Criteria and Surveillance and Management Recommendations. Pediatr Neruol. 2021; doi:10/1016/j.pediatrneurol.2021.07.011.