Information sheet for health professionals helping families of an unborn baby with possible Tuberous Sclerosis Complex (TSC)

Tuberous Sclerosis Australia

This information will help you support families where TSC is suspected in a pregnancy. This often occurs after the discovery of cardiac rhabdomyomas. If these are found prenatally, referral to a maternal fetal medicine service is recommended for further assessment and advice to consider available options.

This information sheet is not intended to be given to families. Tuberous Sclerosis Australia (TSA) publishes information resources specifically written for families with a prenatal diagnosis of TSC. TSA also publishes separate health professional and family information for families with a child newly diagnosed with 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 is the prognosis?

TSC is a highly variable condition. Some people will have significant disabilities caused by TSC, many will have 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.

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 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 that they are unaware that they have TSC. 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.

How is TSC diagnosed?

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].

The most common reason for TSC to be considered prenatally is the discovery of single or multiple cardiac rhabdomyomas. Almost all babies with multiple and around 70% of those with a single cardiac rhabdomyoma have TSC[4].

While it can be difficult to establish a definite prenatal diagnosis, this is useful to ensure that babies with TSC receive early interventions to minimise the risk of seizures. If available, a fetal MRI can be considered to look for cortical tubers, SEN or SEGA. However, the absence of TSC findings does not rule out the diagnosis. Genetic advice should be sought to consider availability of sequencing of *TSC1* and *TSC2*, although this is not routinely offered prenatally. Alternatively, further testing can be planned after the birth of the baby.

Recommendations

1. After prenatal detection of one or more cardiac rhabdomyomas, the possibility of TSC needs to be raised with the parent(s). Further evaluation can include fetal brain MRI if available.
2. Families with a possible or definite diagnosis of TSC should be reviewed by a physician with expertise in TSC. This is so that accurate genetic counselling can be provided and early interventions to minimise risk of seizures can be planned. Contact TSA for assistance with referrals.
3. Children under 2 years old with TSC who have not developed seizures should be actively monitored for signs of seizures, including regular EEG monitoring to look for early electrical signs.

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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.

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Signs and symptoms of TSC

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, however early monitoring and treatment may prevent seizures and reduce their neurodevelopmental impact.

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 the neurodevelopmental outcome for a baby with TSC born today would be better than in previous generations.

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.

Heart

At least 50% of children with TSC have cardiac rhabdomyomas prenatally. 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. Consider fetal echocardiography in patients diagnosed prenatally.

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.

Eyes

Hamartomas can develop in the retina but do not usually affect vision.

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.

Other organs can be affected by TSC and lifelong monitoring is recommended.

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.
- There are recommendations for testing at diagnosis for each sign and symptom of TSC and further recommendations for ongoing surveillance.
- 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).

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

References

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