Epilepsy in Tuberous Sclerosis: Phenotypes, Mechanisms, and Treatments

Anurag Saxena, MD (Pediatrics), MRCPCH1 Julian R. Sampson, DM, FRCP, FMedSci1

1 Division of Cancer and Genetics, Cardiff University School of Medicine, Institute of Medical Genetics, Cardiff, United Kingdom

Abstract

Epilepsy affects 75% to 90% of people with tuberous sclerosis, a multisystem genetic disorder. Although seizures can occur for the first time at any age, onset in infancy or childhood is usual. Around 30% of patients present with infantile spasms that often respond well to treatment with vigabatrin. Later seizures may occur as specific patterns, such as in Lennox–Gastaut syndrome, or with combinations of seizures including focal and multifocal seizures, and drop attacks. Most patients have two or more seizure types. Seizure control using current antiepileptic drugs is often unsatisfactory, leading to frequent polypharmacy. Epilepsy surgery has a place in the management of some patients. Mutations in the TSC1 and TSC2 genes that cause tuberous sclerosis lead to hyperactivation of signaling via the mammalian target of rapamycin complex 1 (mTORC1). Inhibitors of mTORC1 have recently been shown to be effective treatments for some manifestations of tuberous sclerosis; they are now being assessed as potential novel antiepileptic drugs in tuberous sclerosis and related disorders.

Keywords
► tuberous sclerosis
► TSC1
► TSC2
► mTORC1
► epilepsy

Tuberous Sclerosis: A Multisystem Disorder

Tuberous sclerosis, also known as tuberous sclerosis complex (TSC) is a genetic disorder affecting up to 1 in every 6,000 people.1 It is caused by mutations in the TSC1 or TSC2 gene2–3 and is characterized by the development of hamartomatous developmental lesions or growths in many organs. Its clinical manifestations vary between individuals both in terms of the combinations of organs involved and the severity of that involvement. Manifestations are more severe, on average, in TSC2-associated than in TSC1-associated disease.4–7 The emergence of manifestations in different organs is related to age, with some aspects of brain and heart involvement becoming apparent during prenatal development; most manifestations in the skin, kidney, and lung become apparent during childhood or adult life. The diagnosis of tuberous sclerosis can be made according to clinical criteria or by genetic testing (► Table 1).8

Skin signs include hypomelanotic macules and fibrous plaques that often manifest in infancy, facial angiofibromas, and shagreen patches that usually develop later in childhood and periungual fibromas that typically develop in older children and adults.8 Renal involvement is mainly with angiomylipomas that are usually multiple and bilateral. They can enlarge, particularly during adolescence and early adulthood or later, and are associated with hemorrhage, pain, and compromised renal function.9 Around 5% of patients have an early-onset form of polycystic kidney disease due to contiguous deletion of TSC2 and the adjacent PKD1 gene, which when mutated independently, causes autosomal dominant polycystic kidney disease type 1.10 Cardiac rhabdomyomas occur in more than half of infants with TSC. They are often multiple and can be diagnosed by antenatal ultrasound scan. Spontaneous postnatal resolution of cardiac rhabdomyomas is usual, in contrast to other manifestations in TSC.11 Lung involvement with lymphangioleiomyomatosis is usually only clinically significant in adult women, and presents with cough, hemoptysis, shortness of breath, or pneumothorax, and may progress to respiratory failure.12

The central nervous system is involved in virtually all affected individuals and leads to problems including epilepsy, cognitive deficits, autism, and other neurodevelopmental and behavioral disorders, anxiety and depression. These problems...
are rated by patients and their families as the most important consequences of the condition. Epilepsy is the most common symptom of brain involvement and develops in 75% to 90% of people with TSC. Psychiatric problems are underrecognized, and a checklist of TSC-associated neuropsychiatric disorders has been developed recently to improve their detection in the clinic.

18-21 The structural hallmarks of CNS involvement are developmental abnormalities including cortical tubers, subependymal nodules, heterotopic gray and white matter abnormalities,22-21 (►Fig. 1), and brain tumors, termed subependymal giant cell astrocytomas (SEGAs), that typically develop in childhood or early adult life.1 White matter changes on standard magnetic resonance imaging (MRI) feature curvilinear radial bands extending from the ventricles toward the cortex, wedge-shaped lesions, nonspecific focal conglomerate changes, and cerebellar radial bands.22 Diffusion tensor imaging (DTI), a structural MRI technique used to examine the interconnections between different brain regions, is more sensitive than standard MRI in identifying microstructural abnormalities in brain pathways. Recent DTI studies in TSC have shown widespread disorganization in otherwise normal-appearing white matter23,24 and changes in the frontal and parietal lobes that appear to correlate with attention deficits.25

Table 1 Diagnostic criteria for tuberous sclerosis, updated 2012

<table>
<thead>
<tr>
<th>Genetic diagnostic criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>The identification of either a TSC1 or TSC2 pathogenic mutation in DNA from normal tissue is sufficient to make a definite diagnosis of tuberous sclerosis complex (TSC). A pathogenic mutation is defined as a mutation that clearly inactivates the function of the TSC1 or TSC2 proteins (e.g., out-of-frame indel or nonsense mutation), prevents protein synthesis (e.g., large genomic deletion), or is a missense mutation whose effect on protein function has been established by functional assessment (<a href="http://www.lovd.nl/TSC1">www.lovd.nl/TSC1</a>, <a href="http://www.lovd/TSC2">www.lovd/TSC2</a>). Other TSC1 or TSC2 variants whose effect on function is less certain do not meet these criteria, and are not sufficient to make a definite diagnosis of TSC. Note that 10–25% of TSC patients have no mutation identified by conventional genetic testing, and a normal result does not exclude TSC, or have any effect on the use of clinical diagnostic criteria to diagnose TSC.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical diagnostic criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major features</td>
</tr>
<tr>
<td>1. Hypomelanotic macules (≥ 3, at least 5 mm diameter)</td>
</tr>
<tr>
<td>2. Angiofibromas (≥ 3) or fibrous cephalic plaque</td>
</tr>
<tr>
<td>3. Ungual fibromas (≥ 2)</td>
</tr>
<tr>
<td>4. Shagreen patch</td>
</tr>
<tr>
<td>5. Multiple retinal hamartomas</td>
</tr>
<tr>
<td>6. Cortical dysplasiasa</td>
</tr>
<tr>
<td>7. Subependymal nodules</td>
</tr>
<tr>
<td>8. Subependymal giant cell astrocytoma</td>
</tr>
<tr>
<td>9. Cardiac rhabdomyomas</td>
</tr>
<tr>
<td>10. Lymphangioleiomyomatosisb</td>
</tr>
<tr>
<td>11. Angiomyolipomas (≥2)b</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Minor features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. “Confetti” skin lesions</td>
</tr>
<tr>
<td>2. Dental enamel pits (≥ 3)</td>
</tr>
<tr>
<td>3. Intraoral fibromas (≥2)</td>
</tr>
<tr>
<td>4. Retinal achromatic patch</td>
</tr>
<tr>
<td>5. Multiple renal cysts</td>
</tr>
<tr>
<td>6. Nonrenal hamartomas</td>
</tr>
</tbody>
</table>

Definite diagnosis: Two major features or one major feature with ≥2 minor features
Possible diagnosis: Either one major feature or ≥2 minor features

*Includes tubers and cerebral white matter radial migration lines.

TSC1, TSC2, and Signaling via mTORC1

The proteins encoded by TSC1 and TSC2 (referred to as TSC1 and TSC2 or hamartin and tuberin, respectively) form a complex with TBC1D7 within cells that acts as a negative regulator of mammalian (or mechanistic) target of rapamycin complex 1 (mTORC1).26 mTORC1 is activated by amino acids, growth factors, and energy status (AMP/ATP ratio); its best characterized downstream targets include ribosomal protein S6 kinase 1 (S6K1) and eukaryotic initiation factor 4E-binding
protein 1 (4E-BP1), through which protein synthesis is regulated. Other processes regulated by mTORC1 include lipogenesis, angiogenesis, glycolysis, autophagy, inflammatory responses and neuronal migration, differentiation, and function. Loss of functional TSC1/2 leads to overactivation of mTORC1 and perturbation of developmental pathways, the balance of anabolic and catabolic processes and physiological responses to variation in external conditions. Recent research has shown that many (if not all) of the major manifestations of TSC result from overactivation of mTORC1 signaling. The mTORC1 signaling pathway is also dysregulated in diverse disease states, including neurodegeneration, diabetes mellitus, epilepsy, and cancer. Inherited mutations in other components of the signaling pathway cause genetic disorders that are characterized by various combinations of tumor predisposition, cerebral cortical dysplasia, epilepsy, and neurodevelopmental problems.

TSC1 and TSC2 act as tumor suppressors and somatic “second hit” mutations occur in many TSC-associated hamartomas. In the brain, the role of second hit mutations in determining in utero development of cortical tubers is less clear, probably reflecting cellular heterogeneity of these lesions. Nonetheless, there is evidence of upregulated mTORC1 activity in cortical tubers from both adult and fetal brains. Preclinical studies using mouse models suggest that mTORC1 inhibition may normalize aspects of brain development in the context of TSC deficiency, further supporting mTORC1 activation as critical to pathogenesis of structural brain abnormalities in TSC.

Multiple Epilepsy Phenotypes in Infants, Children, and Adults with TSC

Approximately 30% of TSC cases present with infantile spams, the hallmark seizure type of West syndrome, an epileptic encephalopathy syndrome of infancy. Some go on to develop a clinical picture of Lennox–Gastaut syndrome with persisting severe epilepsy. In children and adults with TSC, the typical seizure types are focal and focal dyscognitive seizures, but many also have other seizure semiology such as tonic, clonic, tonic-clonic, myoclonic, atonic, and atypical absences. Unfavorable prognostic factors for epilepsy in TSC include seizure onset in the first year of life, the presence of multiple seizure types, multifocal electroencephalogram (EEG) discharges when awake that generalize in sleep and/or secondary bilateral synchrony, and the onset of new EEG foci during evolution of epilepsy. TSC2 mutations are associated with a significantly earlier presentation of epilepsy than TSC1 mutations, a higher likelihood of infantile spams, and a worse outcome with regards to seizure control and neurodevelopment.

Infantile Spasms in Tuberous Sclerosis Complex

Tuberous sclerosis complex is the most common single cause of infantile spams, accounting for up to 25% of all cases. Their onset in TSC peaks at 4 to 6 months of age, in common with infantile spams from other causes. Infantile spams are characterized by a triad of developmental arrest and/or regression, typical epileptic spasms, and a high-voltage chaotic EEG pattern known as hypsarrhythmia. Irritability may precede the onset of spasms; the affected infant often shows behavioral regression manifesting as indifference to his or her environment and parents, together with cessation or regression of wider developmental abilities. The spasms are usually characterized by bilateral, tonic contraction of muscles in the neck, trunk, and extremities, which may be flexor and/or extensor. The contraction appears to have two phases with an intense, quick phase lasting for a couple of seconds, followed by a longer period of motor arrest during which the posture acquired in the preceding phase is maintained. Some infants may present in a very subtle fashion with head nods, elevation of the shoulders or upward eye deviation, and crying that may be confused with colic.

The spasms typically occur as clusters, and are most likely to be noticed first at the sleep–wake interface. Clusters of spasms may occur a few times per day or up to 100 or more, 5 to 30 seconds apart. There may be many such clusters during a day, and they may be followed by irritability, lethargy, or occasionally an apparent state of hyperaltrerness.

Although infantile spasms in TSC are clinically similar to those due to other causes, there are differences. In TSC the spasms may present very early and be preceded by, or coexist with, focal seizures. Subtle early focal seizures, such as unilateral tonic or clonic phenomena affecting the face or limbs, tonic eye deviation, head turning, and unilateral grimming may go unrecognized until there are more obvious infantile spasms.

Electroencephalogram Findings

Hypsarrhythmia (hypsos—Greek for “high”) is the typical electrophysiological picture in infantile spasms. It is an interictal EEG pattern defined as a diffuse, high voltage (>200 μV), irregular, chaotic mixture of slow waves with sharp waves and spikes. The localization of sharp waves and spikes typically shifts temporally, although in TSC infants it may differ in having an additional consistent focus. This EEG pattern occurs both when awake and in non-rapid-eye-movement (non-REM) sleep, with marked attenuation of the pattern in REM sleep. The typical features of hypsarrhythmia may only be evident during sleep in the initial phase of infantile spasms, making a sleep EEG recording essential. The ictal phase (associated with an epileptic spasm) typically has an initial positive wave over the vertex-central region that evolves into a period of abrupt generalized desynchronization (flattening) called the “electro-decremental response,” lasting for several seconds.

Management of Infantile Spasms

Vigabatrin is very effective in managing infantile spasms due to TSC and is the drug of choice in this situation. If vigabatrin is unavailable or is ineffective, other treatments such as corticosteroids, sodium valproate, topiramate, or zonisamide should be tried. The imperative is to control the seizures quickly. Vigabatrin carries the potentially serious side effect...
of retinal toxicity and permanent peripheral visual field constriction (www.tsalliance.org/documents/VigabatrinAssociatedVisualFieldLossWhitePaper.pdf). This affects some 30% of treated adults, but the risk in children is probably lower. The prevalence of clinically significant visual problems attributable to vigabatrin is much lower, probably 1% to 5%. We do not know either the best surveillance method or the extent to which toxicity may be reversible on stopping treatment. The recommended regular kinetic perimetry for visual field testing is not an option for infants; electroretinogram or optical coherence tomography should be considered. The potential consequences of vigabatrin for vision need to be balanced with the neurodevelopmental consequences of not treating infantile spasms effectively.

Infantile Spasms and Neurodevelopmental Outcome
Infantile spasms in TSC increase the risk of subsequent intellectual difficulties, autism or autism-spectrum disorder, behavioral problems, and epilepsy that is difficult to control. However, several studies have shown that some children with TSC and infantile spasms have normal cognitive outcomes, particularly if seizure control is achieved early. Vigabatrin effectively controls infantile spasms in up to 96% of TSC cases and appears to have a positive impact on neurocognitive outcome. EPISTOP is an ongoing pioneering study in infants with TSC and the first prospective study of epileptogenesis in humans. The trial monitors TSC babies using serial EEGs. Clinicians may use antiepileptic medication (usually vigabatrin) on the basis of a deteriorating EEG before the onset of clinical seizures. The trial will assess the impact on neurodevelopmental outcome over 2 years or more (clinicaltrials.gov identifier NCT02098759).

Lennox–Gastaut Syndrome
Most children developing Lennox–Gastaut syndrome have had prior epilepsy, commonly infantile spasms. The triad of symptoms that develop aged 1 to 8 years are (1) seizures including a mix of myoclonic seizures, tonic, axial tonic, atypical absences, generalized tonic-clonic and focal seizures; (2) an EEG featuring diffuse slow, spike–wave and burst of fast activity during sleep; and (3) learning difficulties and behavioral problems. Most children go on to have refractory epilepsy as adults and are at risk of poor neurocognitive outcomes.

Electroencephalogram Findings
The diagnostic feature is multifocal interictal 2.0 to 2.5 Hz sharp-and-slow wave discharges. Eye opening or photic stimulation do not affect the discharges. The EEG can be activated during sleep, especially in stage 1, 2, and REM sleep, and may sometimes be activated by hyperventilation. The ictal EEG changes depend on the seizure semiology. Tonic seizures are associated with a burst of bilateral rhythmic 10 to 20 Hz activity over anterior areas and the vertex. Atypical absences on the other hand are associated with sharp-and-slow wave discharges, indistinguishable from the interictal phase. Electroencephalogram changes with atonic and atonic–myoclonic seizures show either multiple or diffuse spike-and-slow activity or fast rhythms with an anterior predominance.

Treatment and Outcome
A recent Cochrane review concluded that the optimum treatment for Lennox–Gastaut syndrome remains uncertain, and no study to date has shown any one drug to be highly effective. Rufinamide, lamotrigine, topiramate, and felbamate may be considered as add-on therapies, and clobazam may help for drop seizures. However, total seizure control is rarely achieved.

Epilepsy Associated with TSC in Older Children and Adults
Epilepsy in children and adults with TSC has an unpredictable course. Patients show multiple seizure types, most likely reflecting the presence of multiple tubers with variable epileptogenic potential in most patients. More than half of TSC adults have more than one seizure type, with focal onset seizures in most (93%). At least one third of epilepsy in older children and adults is refractory, despite using multiple antiepileptic medications and nonpharmacological approaches. In comparison to TSC patients with epilepsy who are controlled on medication, the refractory group is characterized by a younger age at diagnosis, a previous history of infantile spasms and/or Lennox–Gastaut syndrome, lower educational achievement, a higher prevalence of psychiatric problems, and association with TSC2 mutations.

Antiepileptic Drugs
Epilepsy management is best coordinated through a multi-disciplinary clinic with specialist expertise in epilepsy because of the frequent association of epilepsy with intellectual difficulties, neurodevelopmental and behavioral problems in patients with TSC, and the frequency of TSC-associated comorbidities, particularly kidney disease. Carbamazepine for focal-onset epilepsy and sodium valproate for generalized and myoclonic seizures are frequently used first-line therapies. Seizure control by monotherapy is relatively infrequent, and combination therapy with medications, including lamotrigine, topiramate, levetiracetam, oxcarbazepine, rufinamide, clobazam, and clonazepam, is often required. The combination of levetiracetam with antiepileptic drugs that enhance GABAergic inhibition, or the combination of sodium valproate and lamotrigine, may be considered. Complicated combinations of antiepileptic drugs rarely provide an additional benefit and can leave a high burden of side effects. It is therefore important to define realistic treatment expectations in "hard-to-treat" patients.

The refractory nature of epilepsy in TSC likely reflects underlying multifocal cortical dysgenesis and perhaps the wider consequences of dysregulated mTORC1 signaling in the brain. The proteins MDR-1 (multidrug resistance) and MRP-1 (multidrug resistance-associated protein-1) are linked to chemotherapy resistance in tumor cells. The presence of these
proteins in cortical tubers suggests they may also play a role in development of refractory epilepsy. Persisting severe epilepsy in the face of expert management with antiepileptic drugs should prompt consideration of nonpharmacological management, including epilepsy surgery, vagus nerve stimulation, or ketogenic diet.

**Epilepsy Surgery**

**Resective Epilepsy Surgery**

It is worth considering resective surgery for patients with refractory epilepsy who have an identifiable epileptogenic zone associated with one or more glioneuronal hamartomas, ideally in noneloquent cortex, even in those (the majority) with multiple cortical tubers. With expert assessment and selection of patients, most cases achieve a meaningful long-term reduction of seizure burden and use less antiepileptic therapy; some cases achieve complete remission.

**Corpus Callosotomy**

Corpus callosotomy may be considered in children who have drop attacks as their most disabling seizure type. Drop attacks (atonic seizures) can occur many times every day and lead to serious injuries. The possibility of inducing a disconnection syndrome through complete callosotomy must be weighed against the dangers and quality-of-life issues posed.

---

Fig. 2  Simplified representation of the signaling pathway upstream of mTORC1 showing disorders associated with mutations affecting the genes encoding pathway components. mTORC1 is composed of mTOR, regulatory-associated protein of mTOR (Raptor) and mammalian lethal with SEC13 protein 8 (LST8). Negative regulators of mTORC1 are shaded dark gray; positive regulators are shaded light gray. Disorders related to epilepsy are indicated in white boxes. Key upstream components in the mTOR signaling pathway include PI3K (phosphoinositide 3-kinase), PTEN (phosphatase and tensin homolog), PDK1 (phosphoinositide dependent protein kinase), AKT (v-akt murine thymoma viral oncogene), AMPK (AMP-dependent protein kinase), TSC1 and 2 (tuberous sclerosis complex 1 & 2). The TSC1/2 protein complex is a major negative regulator of mTORC1 activity. Its function is mediated via TSC2’s inhibition of Rheb. TBC1D7 (TBC1 domain family, member 7) is a third subunit of the TSC1/2 complex. Homozygous mutations in TBC1D7 are associated with macrocephaly, intellectual disability and neuropsychological disorders. PTEN converts the PIP3 (phosphatidylinositol 3,4,5 triphosphate) to PIP2 (phosphatidylinositol 4,5 bisphosphate), thereby reducing activity of PI3K, PDK1 and AKT, which leads to mTORC1 inhibition. A reduction in PTEN activity therefore leads to mTORC1 activation. Mutations of PIK3CA have been identified in patients with megalencephaly–capillary malformation syndrome (MCAP) and hemimegalencephaly (HME), whereas activating mutations of PIK3R2 or AKT3 have been identified in most patients with megalencephaly–polymicrogyria–polydactyly–hydrocephalus syndrome (MPPH) and some with hemimegalencephaly (HME). Truncating mutations in DEPDC5 (disheveled, Egl-10 and pleckstrin domain containing protein 5) have been described in patients with a broad range of focal epilepsy phenotypes: familial focal epilepsy with variable foci (FFEVF), autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), familial temporal lobe epilepsy (TLE), benign epilepsy of childhood with centrotemporal spikes (BECTS) or Rolandic epilepsy, and cases with focal cortical dysplasia (FCD) mediated through the RAS-related GTP-binding protein (RAG) proteins A and C. PMSE syndrome (polyhydramnios, megalencephaly, and symptomatic epilepsy), also known as Pretzel syndrome, results from mutations in STRADA (STE20-related kinase adaptor alpha) that prevents its activation and binding with LKB1 (liver kinase B), resulting in reduction in AMPK-AMP-dependent protein kinase mediated TSC2 activation and hence mTORC1 activation. (Adapted from Saxena A, Sampson JR. Phenotypes associated with inherited and developmental somatic mutations in genes encoding mTOR pathway components. Sem Cell Developm Biol 2014;36:140–146.)
by the seizures. Focal seizures usually persist after callosotomy; such patients may need additional antiepileptic drug treatment and/or secondary surgery to resect the epileptogenic tuber or tubers.66

Vagus Nerve Stimulation

Vagus nerve stimulation is used as an adjunctive therapy for intractable focal-onset seizures in patients aged over 12 years. The antiepileptic effects of vagus nerve stimulation are mediated by altered vagal afferent activities, and probably include altered activities in the reticular activating system, the central autonomic network, the limbic system, and the diffuse noradrenergic projection system.67 Common side effects include cough, hoarseness, voice alteration, and throat paresthesias. It is uncertain whether the efficacy of vagus nerve stimulation in TSC is comparable to other cases with refractory seizures, where there are reported median seizure reductions compared with baseline of 35% at 1 year to 44% at 3 years.68 Studies reporting efficacy of vagus nerve stimulation in TSC-related epilepsy have been small, but suggest that results may be comparable to those achieved in other settings.56,69,70

Ketogenic Diet

A ketogenic diet may be used independently or combined with other treatment modalities to manage difficult-to-treat seizures. It is a high fat, low carbohydrate, and adequate protein diet that results in ketosis; this may exert its antiepileptic effects via mechanisms including enhanced GABA levels, reduced neuronal excitability and firing, stabilization of synaptic function, and inhibition of the mTOR pathway and glutaminergic excitatory synaptic transmission.71,72 A recent Cochrane review of the ketogenic diet in diverse intractable epilepsies in childhood showed short-to-medium term benefits in seizure control comparable to antiepileptic drugs, but poor long-term compliance.73 Studies in adults are very limited.

Pathophysiology of Epilepsy in TSC: Evidence for the Role of mTORC1 Hyperactivation

In conditional transgenic mouse models, homozygous knock-out of TSC1 or TSC2 in various brain cell populations led to hyperactivation of mTORC1 signaling, developmental abnormalities of the brain, seizures, and reduced lifespan.74,75 Brain pathology showed gross enlargement with ectopic, enlarged, and aberrant neurons similar to the dysplastic neurons found in the cortical tubers of TSC. Brain size and the histopathological abnormalities were reversed by treatment with the mTORC1 inhibitors rapamycin and everolimus with cessation of seizures and dramatic effects on survival.76 Elevated mTORC1 activity has also been shown in cortical tubers removed from TSC patients undergoing epilepsy surgery.77 An open-label phase I/II clinical trial suggested that mTORC1 inhibitors present new opportunities for treatment of epilepsy in TSC.78,79 An international multicenter randomized clinical trial, EXIST3 (NCT01713946) is investigating the efficacy and safety of everolimus as an adjunctive therapy in TSC-associated epilepsy.

Role of mTORC1 Hyperactivity in Other Epilepsy-Associated Disorders

A group of related rare disorders is caused by inherited or somatic developmental mutations that affect components of the mTORC1 signaling pathway and that lead to its overactivity (►Fig. 2).34,80–83 These disorders predispose to seizures and include hemimegalencephaly, Pretzel or PMSE (polyhydromnios, megalencephaly, and symptomatic epilepsy) syndrome, megalencephaly–polymicrogyria–polydactyly–hydrocephalus (MPPH) and megalencephaly–capillary malformation (MCAP) syndromes, and the recently described DEPDC5- (disheveled, Egl-10, and pleckstrin domain containing protein 5) associated epilepsies. Overactive mTORC1 activity has also been documented apparently unrelated epilepsy syndromes, such as hippocampal sclerosis and Rasmussen encephalitis.37 These observations suggest that mTORC1 inhibition holds promise for treatment of epilepsy in a diversity of clinical settings.

Conclusions

Epilepsy is an important manifestation of TSC and affects the vast majority of patients with this inherited condition. It is frequently difficult to control, requiring the use of multiple antiepileptic drugs and further measures, including epilepsy surgery in some cases. Early onset of seizures, particularly infantile spasms, is associated with a poor neurocognitive outcome, and the seizures may directly contribute to these problems. Many of the manifestations of tuberous sclerosis are at least in part directly attributable to hyperactivation of mTORC1, and preclinical and early clinical evidence suggest this may also be the case for TSC-associated epilepsy, opening up the possibility of using mTORC1 inhibitors as antiepileptic drugs in patients with TSC.

Acknowledgments

The authors’ research is supported by Wales Gene Park, the Tuberous Sclerosis Association, and Novaris Pharmaceuticals.

References


Laplante M, Sabatini DM. Regulation of mTORC1 and its impact on gene expression at a glance. J Cell Sci 2013;126(Pt 8):1713–1719

Yecies JL, Manning BD. mTOR links oncogenic signaling to tumor cell metabolism. J Mol Med (Berl) 2011;89(3):221–228


Saxena A, Sampson JR. Phenotypes associated with inherited and developmental somatic mutations in genes encoding mTOR pathway components. Semin Cell Dev Biol 2014;36:140–146


