Special Article

Managing Epilepsy in Tuberous Sclerosis Complex

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ABSTRACT

Epilepsy is very common in tuberous sclerosis complex and occurs in 80 to 90% of affected individuals during their lifetime. Onset usually occurs during childhood, and up to one third of children with tuberous sclerosis complex will develop infantile spasms. Although not completely understood, the incidence of epilepsy is thought to relate to the neuropathologic features of the disorder, including cortical tubers and other dysgenetic features. Individuals with tuberous sclerosis complex frequently have epileptiform features to their electroencephalograms. Treatment of epilepsy in tuberous sclerosis complex is similar to epilepsy resulting from other causes and includes anticonvulsant medications, the vagus nerve stimulator, and the ketogenic diet. Vigabatrin has been shown to be particularly effective in treating infantile spasms in the setting of tuberous sclerosis complex. Epilepsy surgery has a very important role in the management of children and adults with pharmacoresistant epilepsy in tuberous sclerosis complex. (*J Child Neurol* 2004;19:680–686).

Tuberous sclerosis complex is a multisystem genetic disorder of variable phenotypic expression, with an incidence of about 1 in 5800 live births worldwide.[1] The disorder results from a mutation in the *TSC1* gene in chromosomal region 9q34 or the *TSC2* gene in chromosomal region 16p13 and is inherited in an autosomal dominant fashion, although up to two thirds of cases result from spontaneous genetic mutation.[2,3] The major neurologic manifestations of tuberous sclerosis complex are seizures, autism, developmental delays, including mental retardation, and behavioral and psychiatric disorders.

Epilepsy is the most common presenting symptom in tuberous sclerosis complex and is also the most common medical disorder in tuberous sclerosis complex. Up to 80 to 90% of individuals with tuberous sclerosis complex will develop epilepsy during their lifetime,[4] with onset typically in childhood. The majority of children with tuberous sclerosis complex have onset of seizures during the first year of life, and up to one third of children with tuberous sclerosis complex will develop infantile spasms.

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Almost all seizure types can be seen in a child with tuberous sclerosis complex, including tonic, clonic, tonic-clonic, atonic, myoclonic, atypical absence, partial, and complex partial. Only "pure" absence seizures are not observed. Seizures that appear generalized, both clinically and by electroencephalographic (EEG) characteristics, can have partial onset in tuberous sclerosis complex and therefore might respond to anticonvulsant medications indicated for partial-onset seizures. If such seizures prove difficult to control with anticonvulsant medications and other medical therapies, seizure foci can potentially be identified by neurophysiologic and neuroimaging techniques, making epilepsy surgery a possible treatment.

RELATIONSHIP OF EPILEPSY TO NEUROANATOMIC FEATURES

Epilepsy in tuberous sclerosis complex is thought to relate to the presence of cortical tubers and other neuropathologic features, although the relationship is not well understood. Cortical tubers consist of dysplastic neurons and giant cells, as well as glial components, and it is hypothesized that abnormal activity in these cells leads to epileptogenesis. Although the molecular mechanisms of epileptogenesis are unknown, abnormalities in glutamatergic and γ-aminobutyric acid (GABA) receptor subunits have been identified in cortical tuber samples,[5] and abnormal glutamatergic transport in astrocytes has been observed in mouse models of tuberous sclerosis complex.[6] Several

studies have characterized the neurophysiologic activity of cortical tubers at the time of epilepsy surgery, with some studies finding cortical tubers to be electrically silent but others finding frequent epileptiform activity associated with the tuber or region around the tuber.[7,8]

Given the range of seizure types and severity in individuals with tuberous sclerosis complex, several investigators have tried to relate seizure activity to anatomic correlates. Cusmai et al found a correspondence between topographic magnetic resonance imaging (MRI) and EEG in 26 of 32 patients with tuberous sclerosis complex studied; all patients had large cortical tubers on MRI.[9] EEG foci without corresponding cortical tubers were identified in 4 of the patients; large cortical tubers without corresponding EEG foci were also observed in 11 of the patients, mainly involving the frontal lobes. Curatolo et al found that the age at which seizures and epileptiform activity develop was related to the location of the cortical tubers identified on MRI, with an earlier expression for temporo-occipital regions than for frontal ones.[10] Goodman et al performed a meta-analysis of the published literature to address the question if the tuber number correlated with the severity of the epilepsy or the age at seizure onset.[11] They compared five independent studies, which showed that the cortical tuber count, as identified by MRI, was higher in individuals with tuberous sclerosis complex with severe disease. They found that the MRI-detected tuber count was six times more likely to be above the median count in patients with severe central nervous system involvement (defined as poor seizure control, moderate mental retardation, or both). However, studies have also shown that up to 10% of individuals with tuberous sclerosis complex with intractable epilepsy have normal brain MRIs, with no evidence of cortical tubers or other dysgenetic features.

EEG CHARACTERISTICS OF TUBEROUS SCLEROSIS COMPLEX

Several investigators have characterized the EEG patterns in individuals with tuberous sclerosis complex. Westmoreland examined EEG findings from 361 patients with tuberous sclerosis complex ranging in age from 2 days to 63 years.[12] A high incidence of abnormalities was identified, with 78% of the patients having epileptiform features. Approximately 12% of the population had a normal EEG, and 10% had slow-wave abnormalities. Of those with epileptiform features, 35% had focal spike or sharp-wave discharges, 33% had multifocal epileptiform discharges, 22% had hypsarrhythmia, and 10% had apparent generalized spike-and-wave discharges. A similar study of 60 patients with tuberous sclerosis complex evaluating over 320 EEG recordings found the most common abnormality to be diffuse slowing, seen in 84% of the recordings. Slow spike-and-wave discharges were seen in 42%, focal spikes in 16%, multifocal spikes in 16%, and normal findings in 8%.[13]

TREATMENT OF EPILEPSY IN TUBEROUS SCLEROSIS COMPLEX

Treatment of seizures in tuberous sclerosis complex is similar to that of epilepsy from other causes, and anticonvulsant medications are the mainstay of treatment. Increasing experience with the newer anticonvulsant medications, especially in the pediatric population, is being obtained in the treatment of epilepsy owing to tuberous sclerosis complex and other causes. As discussed below, vigabatrin has been shown to be particularly effective in treating infantile spasms owing to tuberous sclerosis complex. There have also been a few reports suggesting the efficacy of certain anticonvulsant drugs in the treatment of other seizure types related to tuberous sclerosis complex. Topiramate, lamotrigine, oxcarbazepine, and levetiracetam have all been found to be effective and well tolerated in small populations of individuals with tuberous sclerosis complex and epilepsy.[14–17] Owing to the small size of these studies, it is not yet possible to identify certain anticonvulsant drugs as "drugs of choice" in seizures related to tuberous sclerosis complex other than infantile spasms.

Unfortunately, many children and adults with tuberous sclerosis complex develop seizure disorders that prove to be pharmacoresistant, which is not surprising given the hypothesis that epilepsy results from the associated cortical dysgenesis. One mechanism of refractory epilepsy in tuberous sclerosis complex likely relates to cellular mechanisms of drug resistance because both multidrug resistance transporters *MDR1* and multidrug resistance–associated protein 1 have been shown to be expressed in some cortical tubers.[18]

Alternative treatments to anticonvulsant medications should be considered in patients with tuberous sclerosis complex when seizures cannot be effectively controlled. Current nonpharmacologic treatments include the vagus nerve stimulator, the ketogenic diet, and resective epilepsy surgery.

Vagus Nerve Stimulation

The vagus nerve stimulator was approved in 1997 by the US Food and Drug Administration (FDA) for use in individuals 12 years and older with intractable partial-onset epilepsy; subsequently, over 20,000 stimulators have been implanted worldwide. The only published study assessing the efficacy of the vagus nerve stimulator in tuberous sclerosis complex was by Parain et al,[19] who conducted an open-label retrospective multicenter study evaluating the efficacy of the vagus nerve stimulator in patients with tuberous sclerosis complex. The study involved the review of all children with tuberous sclerosis complex who had the vagus nerve stimulator implanted and operational for at least 6 months in five pediatric epilepsy centers and compared the data with controls with epilepsy from other causes obtained from the Cyberonics vagus nerve stimulator patient registry and other published series of epilepsy surgery. They identified 10 patients with tuberous sclerosis

complex with the vagus nerve stimulator; 9 of the patients had a greater than 50% reduction in seizure frequency, and 5 of these experienced a > 90% reduction in seizures. They concluded that the vagus nerve stimulator is effective in promoting seizure control in tuberous sclerosis complex, although the outcomes were not as positive as those obtained in the published series of epilepsy surgery in tuberous sclerosis complex.

Ketogenic Diet

Another very effective nonpharmacologic treatment for pharmacoresistant epilepsy is the ketogenic diet, which has had widespread clinical use over the past 80 years, particularly in pediatric epilepsy. Based on observations that starvation resulted in improved seizure control, the ketogenic diet was developed to mimic starvation and change the body's main energy source from carbohydrates to fats. Over 20 retrospective and prospective studies have been published evaluating the clinical efficacy of the ketogenic diet in children over the past 80 years, including 4 publications in the past 4 years. All of these studies have shown the ketogenic diet to be an effective treatment for medically intractable epilepsy in childhood and for various seizure types and etiologies.[20] Unfortunately, there are no published reports specifically addressing the efficacy of the ketogenic diet in individuals with tuberous sclerosis complex. In our experience, the ketogenic diet can be an effective treatment for intractable epilepsy in the setting of tuberous sclerosis complex, with efficacies similar to those in seizures from other etiologies.

Resective Epilepsy Surgery

The role of resective epilepsy surgery in tuberous sclerosis complex has been somewhat controversial, owing largely to the fact that many patients have multiple cortical tubers, not a single identifiable epileptogenic "lesion." In addition, it can often prove very difficult and not possible to lateralize or localize the seizure onset in many individuals with tuberous sclerosis complex using conventional presurgical evaluative techniques such as continuous video-EEG monitoring or MRI. EEG monitoring often reveals multifocal epileptiform abnormalities; seizure onset is often difficult to correlate with a discrete EEG change or is associated with apparent generalized or bilateral and multifocal abnormalities. However, multiple clinical series have shown that resective epilepsy surgery is often associated with significant improvement in children and adults with tuberous sclerosis complex, including seizure freedom.[8,21–27] Several investigators have been exploring the utility of other functional and metabolic neuroimaging and neurophysiologic modalities, such as diffusion-weighted MRI, positron emission tomography, single-photon emission computed tomography, and magnetoencephalography, to identify the "epileptogenic tuber" or epileptogenic zone in patients with tuberous sclerosis complex.[8,28–35]

EPILEPSY IN TUBEROUS SCLEROSIS COMPLEX: INFANTILE SPASMS

Approximately one third of children with tuberous sclerosis complex will develop infantile spasms, although some reports suggest an incidence as high as 75%.[36–40] Tuberous sclerosis complex is thought to be the most common single cause of infantile spasms, and in some series, 25% of symptomatic infantile spasms are secondary to tuberous sclerosis complex. Similar to other reports,[40] in our experience, there is a strong association between increasing cortical tuber count and the presence of infantile spasms.

The clinical aspects of infantile spasms in tuberous sclerosis complex are similar in many respects to infantile spasms from other causes. The age at onset of infantile spasms in tuberous sclerosis complex peaks between the fourth and sixth month of life, although onset can occur as early as the second month of life.[41] Partial onset seizures precede infantile spasms in approximately one third of patients with tuberous sclerosis complex who develop infantile spasms.[39,42] Clinically, the spasms themselves can appear to be more subtle than classic flexor or extensor spasms and can appear to be asymmetric, similar to infantile spasms seen in other situations with cortical dysgenesis. Infantile spasms in tuberous sclerosis complex can be flexor, extensor, or mixed and can have lateralizing features such as head turning, tonic eye deviation, and asymmetric or unilateral involvement of extremities. Similarly to infantile spasms from other etiologies, the baby often develops an "indifference" to her or his environment and parents and a change in personality, with increased irritability either coincident to or preceding the onset of infantile spasms. Parents often observe a plateau or even regression in developmental abilities correlating to the onset of infantile spasms and the appearance of this "indifference." There is a strong association between the presence of infantile spasms in tuberous sclerosis complex and subsequent developmental impairment, as discussed below, although children with tuberous sclerosis complex and infantile spasms can have a normal cognitive outcome.[43]

The EEG in infantile spasms owing to tuberous sclerosis complex often shows hypsarrhythmia or modified hypsarrhythmia. However, it is important to realize that the EEG, although typically abnormal, frequently does not have the features of hypsarrhythmia, and in some series, up to 70% of children with tuberous sclerosis complex and infantile spasms do not have the characteristics of hypsarrhythmia.[39] In addition, it should be remembered that hypsarrhythmia is an awake interictal pattern and that even in the presence of hypsarrhythmia, the EEG can appear to be close to normal during rapid eye movement (REM) sleep. Therefore, careful attention must be paid in interpreting the clinical features and the EEG characteristics of an infant with paroxysmal movements, particularly if tuberous sclerosis complex is known or suspected. Other features that can be observed

on EEG in the setting of infantile spasms and tuberous sclerosis complex include one or more foci with spikes activated in slow-wave sleep into diffuse discharges. Ictal correlates are characterized at onset by a focal discharge of spikes and polyspikes originating from the temporal, rolandic, or occipital regions followed by a generalized slow wave and then an abrupt generalized desynchronization in EEG background activities that last up to several seconds.[44]

INFANTILE SPASMS IN TUBEROUS SCLEROSIS COMPLEX: ROLE OF VIGABATRIN

There is convincing evidence in the medical literature that vigabatrin, an irreversible GABA transaminase inhibitor, should be the drug of choice in the treatment of infantile spasms owing to tuberous sclerosis complex. Particularly because vigabatrin has not been approved for clinical use by the FDA in the United States, other treatments can also be used if vigabatrin is not available or proves to be ineffective, including corticotropin (ACTH) and the ketogenic diet, as well as other anticonvulsant medications, such as valproate, topiramate, or zonisamide. If infantile spasms in tuberous sclerosis complex prove to be intractable to medical treatment, then epilepsy surgery should also be considered if an epileptogenic region can be identified.

Several reports in the literature have addressed the efficacy of vigabatrin in infantile spasms, many specifically focusing on tuberous sclerosis complex.[45–49] Hancock and Osborne reviewed 10 published studies assessing the efficacy of vigabatrin in infantile spasms.[45] With vigabatrin treatment, the studies showed a 54% cessation in infantile spasms in 313 children without tuberous sclerosis complex, but in 77 children with tuberous sclerosis complex, there was a 95% complete cessation of infantile spasms. They concluded their review by suggesting that vigabatrin should be offered as first-line therapy in infantile spasms. Mackay et al performed an evidence-based analysis of the established medical treatment regimen for infantile spasms.[47] They surmised a natural history of infantile spasms from clinical studies of infantile spasms in the precorticosteroid era and compared different medical regimens by assessing treatment trials of infantile spasms from 1958 to the present. Evidence of the efficacy of various treatment regimens was defined as class I, II, or III evidence according to established criteria. They concluded that class I and class III evidence existed in published studies, which supported the standard of practice recommendation for the use of vigabatrin in the treatment of infantile spasms with tuberous sclerosis complex.

Chiron et al performed a randomized trial comparing vigabatrin and hydrocortisone in infantile spasms owing to tuberous sclerosis complex.[48] The study design involved a prospective randomized multicenter study using both drugs as monotherapy in patients newly diagnosed with infantile spasms. In their study, all 11 vigabatrin-treated patients became seizure free. Vigabatrin as an initial therapy for infantile spasms was investigated by a European retrospective study in evaluating 250 infants diagnosed with infantile spasms.[49] In this group, there was a 96% response rate in infantile spasms owing to tuberous sclerosis complex, which reflected the most positive response.

Unfortunately, although the efficacy of vigabatrin has been well established in the literature, its use has been limited by many practitioners, in part owing to possible ophthalmic toxicity of the medication. Currently, it is appreciated that ophthalmologic toxicity does occur in a population of individuals exposed to vigabatrin; however, the incidence of such toxicity is unclear, and it is unknown if there are certain risk factors for toxicity, including the relationship to the dose and the relationship to the length of exposure. It is also uncertain if such toxicity is reversible or irreversible following discontinuation of vigabatrin. The electroretinogram is the most sensitive measure of vigabatrin toxicity; if toxicity is present, the full-field electroretinogram shows a reduction of the 30 Hz flicker cone b-wave amplitude.[50–53] These findings are thought to suggest that vigabatrin might have an effect on the inner electroretinal function at the level of the Müller cell. Kinetic perimetry can also be performed in individuals able to cooperate in the study and can show concentric visual field defects in the presence of vigabatrin ophthalmologic toxicity. The electro-oculogram studies have also suggested an effect of vigabatrin on outer retinal function, which might be reversible after vigabatrin treatment is discontinued.[51] In the presence of presumed vigabatrin ophthalmologic toxicity, there is typically a normal appearance to the fundus and macula, although there have been some reports of retinal pigmentary changes.

If vigabatrin is used for infantile spasms, dosing is typically between 100 and 200 mg/kg/day, titrated up over several days. The duration of treatment is typically 1 year, although many clinicians are investigating the efficacy and tolerability of shorter treatment periods owing to the risk of ophthalmologic toxicity. Many physicians suggest that children on vigabatrin be followed by electroretinograms every 6 months to 1 year throughout the treatment course. In many patients, partial seizures can persist following control of infantile spasms by vigabatrin; often combination therapy with other anticonvulsant drugs can be effective in controlling other seizure types.

IMPACT OF INFANTILE SPASMS AND EPILEPSY ON COGNITION IN TUBEROUS SCLEROSIS COMPLEX

Epilepsy, particularly with onset during infancy, and infantile spasms are thought to be risk factors for subsequent neurocognitive impairments and mental retardation in children with tuberous sclerosis complex.[54,55] Joinson et al performed detailed psychometric evaluations on 108 patients with tuberous sclerosis complex and found a bimodal distribution of cognition, with 40% of the population having severe or profound learning disabilities.[56] The remainder of the population was found to function within the normal range

of cognition. Risk factors for more significant cognitive impairment included early-onset epilepsy, particularly infantile spasms. Studies have also shown a higher incidence of autism in children with tuberous sclerosis complex who have early-onset intractable epilepsy and infantile spasms.[57,58] Bolton et al found that increased risk of autism was associated with features of the child's epilepsy, including the presence of temporal lobe epileptiform discharges on EEG, younger age at onset of seizure activity, and a history of infantile spasms.[57]

However, several studies have also shown that children with tuberous sclerosis complex who have early-onset epilepsy and infantile spasms can have a normal cognitive outcome if the seizures are effectively controlled.[40,59–61] Vigabatrin treatment has been shown to result in improved cognitive outcome following infantile spasms in patients with tuberous sclerosis complex, likely reflecting a positive impact of effective seizure treatment.[61] Therefore, it is likely that early and effective control of infantile spasms and other seizure activity can improve developmental outcomes in children with tuberous sclerosis complex.

MANAGING EPILEPSY IN TUBEROUS SCLEROSIS COMPLEX: WHAT WE DO NOT KNOW BUT WOULD LIKE TO KNOW

Epilepsy is very common in individuals with tuberous sclerosis complex and, of course, represents a very significant problem because the seizure activity can also profoundly impact neurocognitive development in children with tuberous sclerosis complex. Although substantial efforts have been made to characterize epilepsy in tuberous sclerosis complex, many questions are left unanswered. Why do individuals with tuberous sclerosis complex have seizures? Although the majority of individuals with tuberous sclerosis complex do experience seizures during their lifetime, a significant population of individuals with tuberous sclerosis complex do not. Some individuals with tuberous sclerosis complex become seizure free and are eventually tapered off medications; others develop highly intractable seizure disorders that are not controlled by anticonvulsant medications, nonpharmacologic treatments, or epilepsy surgery.

The factors that influence the incidence and intractability of epilepsy in tuberous sclerosis complex are poorly understood. Although cortical tubers are thought to somehow be involved in epileptogenicity, it is unclear if all tubers are potentially epileptogenic because many individuals with tuberous sclerosis complex will have multiple cortical tubers but only one region of epileptogenicity. In addition, it is unclear if seizures are produced by the dysgenetic cells of the tuber or if instead (or in addition) these cells are somehow "irritating" to their neighboring neurons. And given that some individuals with tuberous sclerosis complex never experience seizures but have multiple cortical tubers, are there factors that put certain individuals with tuberous sclerosis complex at higher risk of seizures? In addition, do individuals with tuberous sclerosis complex have one or many epileptogenic tubers, and do all of the tubers have epileptogenic potential?

Clinically, there are also several unanswered questions regarding epilepsy in tuberous sclerosis complex. Is it possible to predict pharmacoresistance or intractability sooner in the course of the disease to allow earlier implementation of nonpharmacologic treatment or epilepsy surgery? Is there a role for prophylactic management? Epilepsy occurs in up to 90% of individuals with tuberous sclerosis complex; would it therefore be beneficial to treat individuals once diagnosed with tuberous sclerosis complex, regardless of whether they have a history of clinical seizure activity? Would it be beneficial to treat all infants diagnosed with tuberous sclerosis complex with vigabatrin because roughly one third of them will develop infantile spasms? Why are infantile spasms so common in this population, and why do some children with tuberous sclerosis complex and infantile spasms have a good neurocognitive outcome?

In summary, epilepsy is the most common medical disorder in tuberous sclerosis complex. It is particularly a major issue in childhood because the majority of individuals with tuberous sclerosis complex have seizure onset during the first year of life. Infantile spasms are extremely common in tuberous sclerosis complex; therefore, it could be argued that every child with tuberous sclerosis complex who has onset of paroxysmal movements during infancy has infantile spasms until proven otherwise. In addition, it could be argued that every child with infantile spasms has tuberous sclerosis complex until proven otherwise, given that it is the most common etiology of infantile spasms. Importantly, it should be realized that children with tuberous sclerosis complex can have a good cognitive outcome regardless of epilepsy, even in the presence of infantile spasms.

There are probably several different mechanisms of epileptogenesis in tuberous sclerosis complex, some related to tubers and cortical dysgenesis and possibly others that are not. Efforts to understand epilepsy in tuberous sclerosis complex will broaden and enhance our understanding of the pathophysiology of epilepsy in general.

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