



REVIEW ARTICLE

Tuberous sclerosis complex: a review of neurological aspects

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Tuberous sclerosis complex is characterized by hamartomatous lesions involving skin, brain, kidneys, eyes and heart. Pathologically, tuberous sclerosis is a disorder of cell migration, proliferation and differentiation. Cell lineage and cell migration disorders in the developing cortex of tuberous sclerosis complex patients might produce very different neurological phenotypes including epilepsy, cognitive impairment and autism. Cortical tubers constitute the hallmark of the disease and are pathognomonic of cerebral tuberous sclerosis. Epilepsy is the most common neurological feature, occurring in 96% of patients. Seizures often begin in the first months of life and are frequently severe and intractable. The treatment of seizures has recently benefited from the advent of the new anti-epileptic drugs. Selected drug-resistant patients with tuberous sclerosis complex could be considered for surgical treatment. Clear localization of the most active epileptogenic focus and the zone of the cortical abnormality may lead to tubectomy and improved seizure control in selective drug-resistant patients. The finding of multiple areas of cerebral involvement should not automatically preclude epilepsy surgery in a child with intractable seizures and a well defined seizure origin.

Keywords: Tuberous sclerosis complex. Epilepsy. Mental retardation. Autism.

Introduction

Tuberous sclerosis complex (TSC) is a multisystem autosomal dominant disorder characterized by the widespread development of hamartias, or non-growing lesions, and hamartomas, which grow as benign tumours and rarely progress to malignancy. The most frequently affected organs are brain, skin, kidneys, eyes and heart. It is the unpredictable distribution of these lesions that is thought to result in the broad range of clinical phenotypes observed in TSC even within the same family. The disease affects 1 in 10 000 births and is remarkable for its high spontaneous mutations rate: about 66% of TSC patients have no family history of the disease and appear to represent new mutations.¹

Characterization of the TSC genes

TSC results from mutations in TSC1, the gene on chromosome 9q34, and TSC2, the gene on chromosome 16p13^{2,3} (Table 1). Frequent loss of heterozygosity for alleles in 16p13.3 and rare loss in 9q34 has been found in hamartomas from TSC patients, indicating that a second somatic mutation may be required to produce the TSC phenotype at the cellular level.^{4,5} These findings are consistent with the TSC1 and the TSC2 acting as growth suppressor genes.⁶

The TSC2 gene maps to a gene-rich region of 16p13.3, approximately 2.25 Mb from the telomere and immediately adjacent to the PKD1 gene. The 5.5 kb transcript spans an estimated 43 kb of the

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Table 1. Characterization of the TSC1 and TSC2 genes

	TSC1	TSC2
Localization	9q34	16p13.3
Structure	23 Exons – 8.6Kb transcript alternate splicing in the 5' UTR	41 Exons – 5.5Kb transcript exons 25,26 and 31 alternatively spliced
Mutations	Small truncating mutations	Large deletions/rearrangements Small truncating mutations Missense mutations
Occurrence	10% – 15% of sporadic cases	70% of sporadic cases
Phenotype	? Less mental impairment	?More likely to be mentally retarded Contiguous gene deletion syndrome with PKD1
LOH in hamartomas	Rare	Frequent
Product	Hamartin	Tuberin
Function(s)	?Regulates cell adhesion through inter- action with ezrin and rho ?Regulator/modulator of tuberin activity	GTPase activating protein? Role in the cell cycle
Subcellular localization	Cytoplasmic, ?cortical	Cytoplasmic, ?Golgi associated
Animal models	Knockout mice under development	Eker Rat Knockout mice <i>Drosophila</i> (gigas)

genomic sequence and comprises 42 known exons, of which 41 are coding and encodes an 1807 amino acid protein, called tuberin, with little similarity to other known genes. Near the COOH terminus 163 amino acids are homologous to the catalytic domain of a guanosine triphosphatase (GTPase) activating protein GAP3 (rap1GAP). GAPs are regulators of the GTP binding and hydrolysing activity of the Ras superfamily of proteins that help to regulate cell growth, proliferation and differentiation. The TSC1 gene consists of 23 exons of which the last 21 contain coding sequence. The TSC1 protein, which is called hamartin, consists of 1164 amino acids with a calculated mass of 130 kilodaltons. The protein is generally hydrophilic and has a single potential transmembrane domain at amino acids 127 to 144 as well as a probable 266-amino acid coiled-coil region beginning at position 730.^{3,7}

The mutations observed in TSC1 consist of small deletions, small insertions and point mutations. The majority of mutations are likely to inactivate protein function and these findings support the hypothesis that TSC1 functions as a tumour suppressor gene. At the moment, about 350 different mutations in both TSC genes are known. There is an equal distribution of mutations between TSC1 and TSC2 among familial cases, while among sporadic cases, TSC2 mutations are much more frequent than TSC1 mutations. The wide range of tissues in which TSC associated hamartomas develop implies a fundamental role for both TSC genes in regulating cell proliferation and differentiation. Furthermore, the high clinical variability within families in which a single mutation must be segregating suggests that

strong correlations between a particular genotype and the clinical phenotype are unlikely. Sporadic patients with TSC1 mutations had, on average, milder disease in comparison with patients with TSC2 mutations. They had a lower frequency of seizures and moderate-to-severe mental retardation, fewer subependymal nodules and cortical tubers, less-severe kidney involvement, no retinal hamartomas, and less severe facial angiofibroma.⁸ Moreover, TSC2 mutations are associated with a significantly earlier presentation of epilepsy than in TSC1 mutations, which results in frequent infantile spasms.⁹ Although there was overlap in the spectrum of many clinical features, grade 2–4 kidney cysts or angiomyolipomas, forehead plaques, retinal hamartomas, and liver angiomyolipomas, were very rare or not seen at all in TSC1 patients.⁸ Parents with multiple children with TSC and no clinical features of the disease, are more likely to have germline mosaicism than non-expression of the mutation.

Pathological findings

Pathologically, TSC is a disorder of cell migration, proliferation and differentiation.¹⁰ Present evidence suggests that the central nervous system lesions of TSC are due to a developmental disorder of neurogenesis and neuronal migration. Two populations of neuroepithelial cells are generated by the germinal matrix in TSC. One is a population of

neuroblasts that form normal neurons and astroglia and that migrate to the cortical plate where they form histologically normal cerebral cortex. The second is an abnormal cell population that forms primitive cells which often fail to show clear neuronal and glial differentiation. Some of these cells, named 'neuroastrocytes', remain in the germinal matrix zone where they form subependymal nodules and giant cell tumours. Some neuroastrocytes show partial migration, forming heterotopia in the subcortical white matter. More differentiated cells migrate to the cortical plate where they form aggregates of dysplastic cortex, the cortical tubers. Cells in tubers share with those in subependymal nodules and giant cell tumours the frequent absence of clear neuronal and glial differentiation, showing features of primitive stellate neurons with few dendritic spines.^{10,11} Tuberin and hamartin are widely expressed in human fetal tissues. These evidences suggest a critical function of these two proteins in early development and maturation of the brain. Tuberin was undetectable from subependymal giant cell astrocytoma examined in three patients suggesting that a complete inactivation of tuberin expression is associated with tumour development.¹² It remains still unknown how a deficiency of GAP activity for Rap 1 or rab5, if that is the critical function of tuberin, leads to hamartoma development. The mechanism by which loss of hamartin expression produces TSC lesions is also unclear. Recently it has been reported that hamartin regulates cell adhesion interacting with the Ezrin-Radixin-Moesin family of actin-binding proteins. This interaction is essential for activation of the small GTP-binding protein Rho. These data suggest that a loss of hamartin cause the disruption of cell-matrix adhesion that in turn may induce initial development of TSC hamartomas. Therefore, in this case, Rho-mediated signalling pathway regulating cell adhesion may constitute a rate-limiting step in tumour formation.¹³

It is likely that hamartin and tuberin participate in the same pathways of cellular growth control and share a common biochemical pathway. The proteins appear to co-localize at the cellular level and recent evidences suggests that there is a direct binding between tuberin and hamartin. These two proteins form a cytosolic complex interacting at the N-terminal ends of both protein. This interaction is abolished by some TSC-associated mutations.¹⁴ A mutation of either proteins would therefore be sufficient to inactivate the complex and lead to the pathology seen in patients with TSC. The tuberin amino acid substitutions N525S, K599M and R905Q do not affect the interaction with hamartin. In

contrast, the tuberin missense changes R611Q, R611W, A614D, F615S, C696Y and V769E prevent the interaction with hamartin. These data suggest that the central region of tuberin, containing the amino acids R611, A614, F615, C696 and V769, is important for maintaining the correct interaction with hamartin and in regulating the post-translational modification status of tuberin.¹⁵

Diagnostic criteria

In light of new clinical and genetic information, the clinical features of TSC are now classified into *major* and *minor* features. The major features include the signs that have a high degree of specificity for TSC, while the minor category includes the less-specific findings and the less-substantiated signs (Table 2). By these revised clinical diagnostic criteria, the presence of two major features or one major plus two minor features constitutes a definitive diagnosis of TSC. One major plus one minor feature indicates a probable diagnosis of TSC, whereas either one major feature or two or more minor features suggests possible TSC.¹⁶ Because of the great variability of clinical expression and severity of TSC and the absence of a reliable molecular marker of the disease, diagnosis can be difficult in patients with only subtle manifestations. The

Table 2. Diagnostic criteria for tuberous sclerosis complex

Major features	
1.	Facial angiofibromas or forehead plaque
2.	Non-traumatic unguial or periungual fibroma
3.	Hypomelanotic macules (three or more)
4.	Shagreen patch (connective tissue naevus)
5.	Multiple retinal nodular hamartomas
6.	Cortical tuber
7.	Subependymal nodule
8.	Subependymal giant cell astrocytoma
9.	Cardiac rhabdomyoma, single or multiple
10.	Lymphangiomyomatosis and/or renal angiomyolipoma
Minor features	
1.	Multiple, randomly distributed pits in dental enamel
2.	Hamartomatous rectal polyps
3.	Bone cysts
4.	Cerebral white matter radial migration lines
5.	Gingival fibromas
6.	Non-renal hamartoma
7.	Retinal achromic patch
8.	'Confetti' skin lesions
9.	Multiple renal cysts

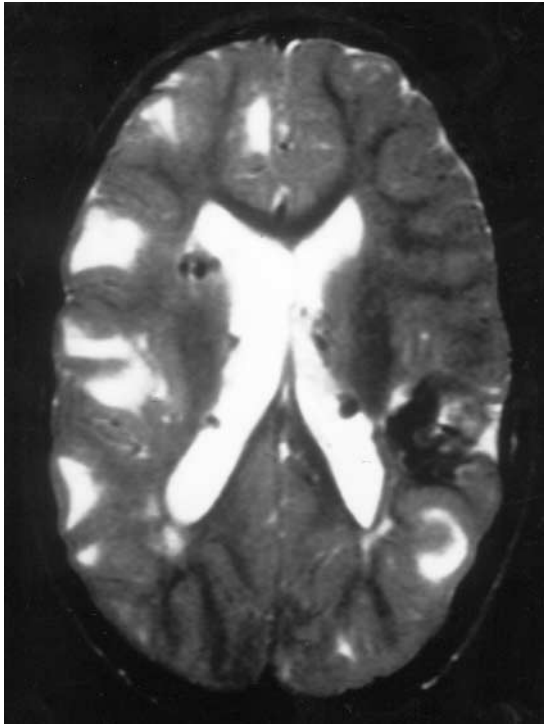


Fig. 1a. T2 weighted MRI scan from a severely retarded boy with poorly controlled seizures reveals multiple increased signal lesions of the subcortical white matter and cortex, and nodular subependymal lesions.

diagnostic criteria for TSC are age dependent. In fact, the most specific findings for TSC become evident in older children, while the diagnosis of TSC is difficult in children below 2 years of age, in which the majority of skin and visceral lesions are undetectable. In this group, hypomelanotic macules and infantile spasms still remain useful in diagnosis. Since the frequency of symptoms increases with age, the usefulness of diagnostic criteria is significantly limited for early diagnosis in some paediatric patients.¹⁷

Neurological phenotypes

Abnormalities of neuronal migration and cellular differentiation, and excessive cell proliferation all contribute to the formation of the various brain lesions of TSC and to the production of very different neurological phenotypes. Magnetic resonance imaging (MRI) studies provide excellent *in vivo* demonstration of the various pathological lesions. An especially interesting finding is the frequent demonstration of abnormal wedges of tissue extending from the subependymal zone to the cerebral cortex, and including cortical tubers,

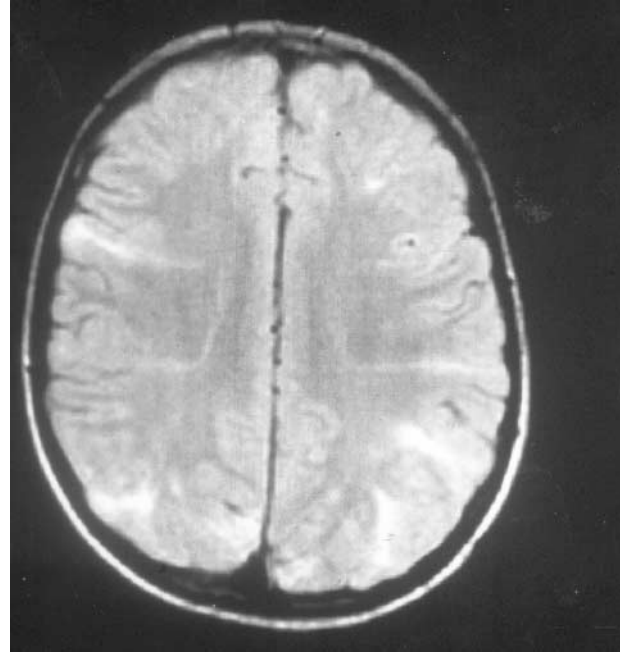


Fig. 1b. T2 weighted MRI scan reveals linear increased signal lesions perpendicular to the cerebral cortex.

subependymal nodules, and radial hypomyelinated tracts extending from subependymal area to the cortex Figs 1a, 1b.

Cortical tubers constitute the hallmark of the disease and are pathognomonic of cerebral TSC. The number and localization of cortical tubers may account for the variability of the neurological phenotype observed in TSC patients. Symptoms of cortical tubers include seizures, mental retardation, learning disabilities, attention deficit disorders with hyperactivity, and autism. A small proportion of children with TSC have motor deficits, mainly spastic hemiparesis. A double hemiparesis may rarely be observed when bilateral tubers are present in the motor cortex. Subependymal giant cell astrocytomas (SEGAs) are histologically benign tumours that develop in 6 to 15% of subjects with TSC. They arise from a subependymal nodule in the lateral ventricles, near the foramen of Monro. They can be locally invasive often causing progressive neurological dysfunction, such as new focal neurological deficit, behavioural change, exacerbation of seizures and increased intracranial pressure with headaches and blurred vision. Early diagnosis is made with computed tomography (CT) or MRI using contrast enhancement because the tumours fill with the contrast marker. In patients with SEGAs, brain imaging should be performed every 3 to 6 months to identify enlarging tumours and to monitor their growth.

Epilepsy

Seizures are the most common neurological symptom of TSC, occurring in 96% of children aged from 9 to 14 years referred to a Child Neurological Clinic.^{17,18} Cortical tubers detected by MRI as high-intensity signal areas represent the epileptogenic foci of TSC, and a topographic relationship exists between electroencephalogram (EEG) abnormalities and the largest MRI high-signal lesions.^{18,19} MRI lesions in the occipital lobes show the best correlation with the EEG foci, whereas the weakest correlation is with frontal lesions. Fluid-attenuated inversion recovery images have been shown to be more sensitive for the detection of small subcortical and gyral core tubers, most of which were overlooked or misdiagnosed as the partial volume effect of the cerebrospinal fluid (CSF) on conventional T2-weighted images.²⁰ Positron emission tomography (PET) may reveal hypometabolic regions not predicted by MRI, demonstrating that the disturbance of cerebral function may be more extensive than indicated by morphological studies alone.²¹

Epilepsy in TSC often begins during the first year of life and, in most cases, in the very first months. The high incidence of infantile spasms and hypsarrhythmia has long been emphasized, but it is now clear that infants with TSC are clinically and electroencephalographically different from those with classical infantile spasms and hypsarrhythmia.²² In the same child partial seizures may precede, coexist with, or evolve into infantile spasms. Many forms of subtle partial seizures, such as unilateral tonic or clonic phenomena mainly localized in the face or limbs, and other seizures with subtle lateralizing features, such as tonic eye deviation, head turning, and unilateral grimacing, can occur frequently but may be missed by the parents until the 3rd or 4th month of life when infantile spasms occur. The EEG at onset shows multifocal or focal spike discharges and irregular focal slow activity. Video-EEG monitoring and polygraphic recordings of the infantile spasms have shown that each spasm consist of a combination of both focal and bilateral manifestations. Although the pathophysiological mechanisms responsible for the coexistence of infantile spasms and partial motor seizures are still uncertain, infantile spasms associated with TSC may be of focal nature, suggesting a rapid secondary generalization of partial seizures. The age at seizure onset and the age when epileptiform activity becomes apparent on the EEG depend on the location of the cortical tubers detected by MRI

and may coincide with functional maturation of the cortex, with an earlier expression for temporo-occipital regions than for frontal ones.²²

A number of young children with TSC who present with partial seizures or infantile spasm at onset, later develop intractable seizures with multifocal EEG abnormalities associated with bilateral and more synchronous slow spike-wave complexes and an electroclinical pattern that resembles a Lennox-Gastaut syndrome. At this stage it is difficult to recognize a focal origin of these apparently generalized abnormalities on visual inspection of the tracings due to the presence of apparently bisynchronous EEG abnormalities. This phenomenon is particularly frequent for discharges originating in the frontal regions and followed by secondary bilateral synchrony. Frontal seizures are often characterized by apparently bilateral clinical manifestations corresponding to a rapid electrographic generalization suggestive of bilateral cortico-cortical interactions. In patients with TSC, the differential diagnosis between LGS and localization related symptomatic epilepsy originating in the frontal lobe may be extremely difficult and only in few cases long-term video-EEG monitoring can reveal subtle electroclinical manifestations suggestive of a focal seizure onset.²³ In these patients high time-resolution topographic EEG analysis and dipole localization methods may detect secondary bilateral synchrony, often originating in frontal regions and corresponding to prominent cortical tubers detected by MRI in the mesial surface of the frontal or anterotemporal lobes.

The natural history of epilepsy in patients with TSC, from infancy into childhood tends to be one of increasing seizure frequency and severity, with poor response to the anti-epileptic drugs and a diminished quality of life because of the seizures and adverse medication effects. Unfavourable prognostic factors include onset earlier than 1 year of age, presence of several seizure types (infantile spasms and partial motor or complex partial seizures; drop attacks and atypical absences) multifocal discharges and/or secondary bilateral synchrony, and occurrence of new EEG foci during the evolution.^{19,22}

Mental retardation

Patients with TSC range from intellectually normal to severely retarded. The prevalence of

learning disabilities varies from 38 to 80% and when it does exist, it tends to be moderate or severe in degree. Children with infantile spasms and hypsarrhythmia are reported to be more severely affected than those with any other form of epilepsy.¹⁸ The question arises as to whether seizures cause mental retardation or whether mental retardation and epilepsy in children with TSC are two different aspects of the same underlying brain dysfunction. The relationship between mental functions and number of cortical lesions detected by MRI has been investigated. Although there was considerable variation in the mental functions of patients with five or fewer cortical lesions, the development of all patients with ten or more cortical lesions was severely impaired.^{24,25}

By contrast, no correlation has been found between the severity of mental retardation and the number and size of tubers, including small subcortical and gyral core tubers, detected only on fluid-attenuated inversion recovery images.²⁰ Curatolo *et al.*²² have suggested that both number and localization of cortical tubers play an important role in mental outcome and that epilepsy and mental retardation probably reflect the underlying brain dysfunction caused by the cortical tubers.

Late onset partial seizures or transient infantile spasms were the only seizure types observed in the non-retarded individuals. All patients with favourable evolution of their epilepsy had normal psychomotor development before the onset of the first seizure and usually had only one seizure type. Children with normal intelligence had small, isolated cortical tubers, mainly localized in the parietal and rolandic regions, and a less severe epilepsy. They may have had different specific neuropsychological deficits related to the location of the cortical tubers, even when they were seizure-free. By contrast, patients with stable mental retardation suffered from frequent partial seizures, developing multifocal or secondary generalized epilepsy, and showed multiple bilateral, strategically localized cortical tubers on MRI.

Progressive mental deterioration observed in TSC children with intractable seizures may also be due to a heightened epileptogenicity of parasagittal frontal tubers. Shepherd *et al.*²⁶ reported that fewer tubers in the frontal regions might be a favourable predictor for mental development. The number of cortical tubers detected by MRI has been proved to be a good biomarker for the degree of mental disability.^{25,27} Since the number of tubers are determined very early in the gestational period, it is likely that extensive brain disruption may predetermine which individuals develop poor mental outcome.²⁴

Behavioural phenotypes

In addition to mental retardation, multiple behavioural problems, including sleep disorders, hyperactivity, attention deficit, aggressiveness, and autism, have been found in children with TSC.^{22,28} Sleep disorders, such as night waking, waking early, seizure-related sleep problems, and excessive daytime sleepiness, are considered one of the most common behavioural manifestations in children with TSC.²⁹ Sleep organization of TSC patients are characterized by a reduced rapid-eye-movement sleep, a sleep instability and fragmentation by frequent awakenings. Children with seizures show a more disrupted sleep architecture compared with seizure-free children. Therefore, sleep disorders seems to be mainly due to sleep-related epileptic events.³⁰

An association of TSC and autism is based on the joint occurrence of these two relatively rare disorders. The cause of this association remains unknown. The majority of reported TSC children with autistic-like behaviour had experienced infantile spasms and were mentally retarded, raising the question of cognitive defects as a primary cause of autism and behaviour problems.³¹ Although the pathogenesis of autism in individuals with seizures and mental retardation still remains a puzzle, it is possible that autism, epilepsy, and mental retardation are all different symptoms of the same underlying brain dysfunction. Autism appears to be more common in infants with frontal and temporal tubers, and it has been suggested that an early dysfunction in the associative areas owing to the location of cortical tubers may be responsible for the autistic features.²² At the moment two pathways to autism and related pervasive developmental disorders could be envisaged, one involving the temporal lobes, the other the frontal lobes, perhaps each having similar but distinctive phenotypic profiles.³¹⁻³³ An alternative explanation is that the behavioural phenotype seen in TSC reflects more direct effects of an abnormal genetic programme. The TSC2 gene product tuberin is highly expressed in brain areas involved in the behavioural phenotypes of the autistic disorder, such as in frontal and temporal regions.³⁴ A couple of genome scans in autism suggested that a potential susceptibility gene may be located on chromosome 16p13. The genetic dissection of the short arm of chromosome 16 in autism will help to localize such candidate gene and clarify its position with respect to the TSC2 locus. Positional cloning of susceptibility genes in autism may provide important clues in the understanding of autistic behaviour associated with TSC.³⁴

Medical and surgical treatment

The treatment of seizures in TSC is often difficult and frustrating with a limited response to the conventional anti-epileptic drugs, but has benefited from the advent of the new ones. Chiron *et al.*³⁵ and Aicardi *et al.*³⁶ reported the efficacy of vigabatrin in refractory infantile spasms and the best results were obtained in patients with TSC. Hancock and Osborne³⁷ recently reviewed all studies published in the English language literature investigating the efficacy of vigabatrin in the treatment of infantile spasms. Of the patients affected by TSC, 73 (95%) had complete cessation of their infantile spasms, compared with 169 (54%) of the remaining patients. The effect was observed within 1 week in the majority of patients, a much quicker response than that observed with steroids, benzodiazepines or sodium valproate, which can take weeks to show efficacy. Curatolo³⁸ suggested that in children with TSC vigabatrin could be effective in reducing frequency of focal seizures in up to 74% of patients. However, localization related effectiveness of vigabatrin shows better results on partial seizures originating from parieto-occipital lobes.

Unfortunately, in recent years, there have been several reports published on the appearance of alterations of the visual fields in up to 40–50% of patients treated with vigabatrin.^{39,40} Tong *et al.*⁴¹ have demonstrated that vigabatrin levels are dose-related, but are significantly higher in the retina than in any other brain tissues. Currently, the minimum duration and doses of vigabatrin treatment that can produce this side-effect are unknown and the feasibility of using low dosages and short treatment periods (2–3 months) should be investigated.

However, reversibility of the visual field constriction after vigabatrin drop-out was recently reported.⁴² If recovery from visual field constriction after vigabatrin withdrawal will be confirmed, this finding could permit a prolonged use of vigabatrin in selected patients with tuberous sclerosis.

Topiramate is emerging as a more effective drug in partial seizures with or without secondary generalization and in the Lennox–Gastaut syndrome. Among 14 children with refractory epilepsy and TSC treated for 6 months with topiramate as add-on therapy, seizures were reduced >50% in 64%; three patients had no seizures for 6 months.⁴³ The mechanisms of action of topiramate, apart from state-dependent blockade of sodium and calcium channels, and inhibitory effect on carbonic anhydrase, include the enhancement of γ -aminobutyric acid (GABA) activity on GABA_A receptors with elevation of cerebral GABA

levels, and antagonism of glutamate receptors. For these reasons and for the good preliminary results obtained with topiramate, this can be reported as a promising new agent for the treatment of partial seizures in TSC patients. In most patients with Lennox–Gastaut syndrome a total seizure control may be impossible. In these patients the treatment should be focused on the suppression of the more dangerous seizures (i.e. drop attacks) without producing unacceptable adverse effects and inability to participate in daily living activities. In the future when the biochemical abnormalities of TSC will be better understood, a rational approach to pharmacotherapy directed toward the specific underlying neurotransmitter systems may be finally developed. New drugs delivery systems for delivering small quantities of anti-epileptic drugs directly to targeted brain areas could be a future option.

Selected drug-resistant epileptic patients with TSC and well-defined seizure origin could be considered for surgical treatment. Complete removal of large single cortical hamartomas corresponding to the most active epileptogenic foci can result in either cessation of seizures or better control.^{44,45} The finding of multiple areas of cerebral involvement should not automatically preclude epilepsy surgery in a child with intractable seizures if seizure monitoring reveals seizure-onset from only one anatomic area.⁴⁶

In our experience clear localization of the most active epileptogenic focus and of the zone of the cortical abnormality may lead to tubectomy and improved seizure control in selective drug-resistant patients.²³ The spatio-temporal characterization of EEG phenomena, combined with detailed video-EEG analysis of the ictal episodes and PET/single photon emission computed tomography (SPECT) scanning, can significantly contribute to the pre-surgical assessment and, in the near future, possibly contribute in minimizing the invasiveness of the currently available procedures.⁴⁷ Converging information between video-EEG monitoring, extracranial ictal and interictal localization with MRI fusioning, can improve our ability of selecting candidates who could benefit from surgical treatment.

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