Child's Nerv Syst (1996) 12:515–521

INVITED PAPER

Paolo Curatolo

Neurological manifestations of tuberous sclerosis complex

Received: 24 January 1996

P. Curatolo (✉)
Section of Pediatric Neurology,
University of Rome "Tor Vergata",
Ospedale S. Eugenio,
Piazza Umanesimo, 10,
I-00144 Rome, Italy
Tel.: (39) 6-59 04 28 01
Fax: (39) 6-59 17 415

P. Curatolo
IRCSS, S. Lucia, Rome, Italy

Abstract CNS lesions of tuberous sclerosis complex (TSC) are due to a developmental disorder of neurogenesis and neuronal migration. MRI studies provide excellent in vivo demonstration of the various pathologic lesions. Symptoms of cortical tubers may include seizures, mental retardation, learning disabilities, and abnormal behavior. Seizures have a focal or multifocal origin, this clinical feature depending on the localization of the cortical tubers. Epilepsy associated with TSC is often intractable, but seizure control has benefited from the introduction of the new antiepileptic drugs. Carefully selected drug-resistant patients can be assessed with intensive monitoring as candidates for surgical removal of epileptogenic lesions. The success of epilepsy surgery is predicated on the clear identification of epileptogenic foci.

Key words Tuberous sclerosis complex · Epilepsy · Antiepileptic drugs · Surgery

Introduction

Tuberous sclerosis complex (TSC) is one of the most common neurocutaneous syndromes, with an overall prevalence of approximately 1 in 30,000 and a birth incidence of 1 in 6,000 [26]. TSC is a multisystem autosomal dominant disorder characterized by hamartias, or nongrowing lesions, and hamartomas, which grow as benign tumors, The most frequently affected organs are the skin, brain, kidneys and heart. Sporadic cases account for about two-thirds of all cases of TSC.

Genetic linkage studies performed on families segregating TSC indicate that about half the cases are due to *TSC1*, the gene on chromosome 9q34 and half are due to *TSC2*, the gene on chromosome 16p13 [15, 27]. There is no evidence for a third gene causing TSC. The *TSC2* gene and its protein product, named tuberin, were recently identified [14, 24]. The likely role of tuberin as a GTPase-activating protein is consistent with its proposed function as a tumor suppressor gene [29]. Identification of TSC1 has not yet been achieved, despite intensive efforts in many laboratories. Recent findings also suggest a growth suppressor-like activity for the *TSC1* gene [5]. There are no significant differences in the clinical phenotype associated with *TSC1* vs *TSC2* disease, as defined by analysis of families showing clear linkage to one or the other chromosomal region. 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.

The diagnosis of TSC is not difficult in a patient with the classic features of the disorder. Any one pathognomonic feature is sufficient to establish the diagnosis. These include facial angiofibromas, multiple ungual fibromas, multiple retinal astrocytomas, and histologically confirmed cortical tubers or subependymal nodule or giant cell astrocytoma. Many other signs are less specific for TSC, but a definite or presumptive diagnosis is allowed when two or three features are present [19]. Even some of the findings now considered pathognomonic must be viewed with caution, because there are few population studies to document their specificity for TSC or to allow an estimate of their prevalence in the general population [28]. Because of the wide 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.

Pathologically, TSC is a disorder of cell migration, proliferation and differentiation [22]. Present evidence suggests that the CNS 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 normal 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 tumors. Immunochemical studies have demonstrated that cells in these lesions may have both neuronal and glial markers [20]. Some neuroastrocytes show partial migration, forming heterotopias in the subcortical white matter. More highly 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 tumors the frequent absence of clear neuronal and glial differentiation, showing features of primitive stellate neurons with few dendritic spines [20, 22]. The findings of similar cells at different sites, including the subependymal zone, white matter and cortex, indirectly support the idea that these lesions of TSC result from a migration abnormality. MRI studies provide excellent in vivo demonstration of the various pathologic 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 subependymal nodules, white matter heterotopias and cortical tubers. These lesions provide compelling evidence of defective cell migration in TSC.

Cortical tubers constitute the hallmark of the disease and are pathognomonic of cerebral TSC. The neurologic manifestations are variable. Symptoms of cortical tubers include partial or generalized seizures, mental retardation, learning disabilities, and abnormal behavior. Seizures are the most common neurologic symptom of TSC, occurring in 92% of patients in a large clinical series [18]. Epilepsy associated with TSC is often intractable, but has benefited from the advent of the new antiepileptic drugs. Newer neuroimaging techniques have added to our understanding of symptomatic epilepsies with structural lesions and to strategies for presurgical evaluation of TSC children with intractable epilepsy. Surgery will probably receive more attention in the future; however, the success of epilepsy surgery is predicated on the clear identification of epileptogenic foci [13].

Epilepsy

Epilepsy in TSC often begins during the first year of life and, in most cases, in the very first months. At this time the most common types of seizures are partial motor seizures and infantile spasms. 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 classic infantile spasms and hypsarrhythmia [10]. 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 awake EEG at onset shows multifocal or focal spike discharges and irregular focal slow activity. Although foci can be located in any region of the brain, the most common locations for focal EEG discharges at the age of infantile spasms are the posterior temporal and occipital regions in topographic correspondence with MRI tubers [9, 12]. During sleep, an increase in epileptiform activity is usually observed; the multifocal abnormalities tend to generalize, resembling hypsarrhythmia. Video-EEG monitoring and polygraphic recordings of the infantile spasms have shown that the ictal phenomenon is a single seizure. Each spasm consist of a combination of both focal and bilateral manifestations. The ictal EEG starts with a focal discharge of spikes and polyspikes, often originating from the posterotemporal, rolandic, or occipital regions, followed by a generalized irregular slow transient and an abrupt, diffuse relative flattening of the EEG. 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 a focal nature, suggesting a rapid secondary generalization of partial seizures. This is not surprising given the presence of multifocal lesions, which act as epileptogenic foci in TSC.

The prognosis of infantile spasms is generally poor, and a large majority of patients with infantile spasms at onset later experience either simple partial motor or complex partial seizures, or apparently generalized (tonic, atonic, and tonic-clonic) seizures. Paroxysmal EEG abnormalities may include unifocal spikes and spike-and-wave activity, multifocal spike-and-wave, and bilaterally synchronous or asynchronous slow spike-and-wave complexes. After 2 years of age, additional frontal or anterior temporal epileptic foci progressively appear [10, 12]. During sleep the EEG is characterized by multifocal frontally dominant abnormalities associated with bursts of bilateral and more synchronous slow spike-and-wave complexes, often interpreted as Lennox-Gastaut syndrome. At this stage it is difficult to recognize any focal origin of these apparently gen-

eralized abnormalities, but in our opinion these electroclinical patterns should be considered to be examples of partial epilepsies with secondary bilateral synchrony (SBS) in the great majority of cases. The EEG features necessary for the diagnosis of SBS are the presence of focal epileptiform discharges followed within 100–200 ms by bursts of bilaterally synchronous spike-and-wave complexes. High time-resolution topographic EEG analysis and dipole localization methods may detect SBS, often originating in frontal regions and corresponding to prominent cortical tubers detected by MRI in the mesial surface of the frontal or anterotemporal lobes [11]. Differentiation between symptomatic partial epilepsy with SBS and symptomatic generalized epilepsy of the Lennox-Gastaut type is particularly difficult in patients with frequent and intractable atonic seizures or drop attacks [16]. We found that atonic seizures may result from secondary epileptogenesis in these patients and may have a frontal cortical origin [30]. Single photon emission computed tomography (SPECT) and positron emission tomography (PET) images revealing multifocal areas of cortical hypoperfusion or hypometabolism suggest that these methods may also be useful in distinguishing the two syndromes [6, 33]. This distinction is not of theoretical importance alone. Patients with SBS may profit from callosal section, with relief of drop attacks.

EEG mapping can often help to localize and describe the epileptic foci with more precision, and is a supplementary tool in the presurgical evaluation of epileptic patients. We have recently studied interictal epileptiform activity in 11 children with TSC and epilepsy, using spike voltage topography and a computer-based dipole source localization method [11]. At least 10,400-ms epochs containing one paroxysmal discharge were computed for each subject, and localization of equivalent dipole layers was attempted. We studied the onset of the discharges in six patients with apparently bisynchronous abnormalities with a sequence of maps, using high time resolution. In all cases a lateralized onset was found, with subsequent propagation to the controlateral homologous regions with an average latency of 24 ms. Five children had a frontal and one had a temporal localization, corresponding to the site of a prominent MRI lesion. These findings support the concept that, in most TSC children, apparently generalized spike-and-wave complexes are of focal origin, with subsequent SBS. This has important implications for the clinical management of these patients. In our opinion, multifocal and apparently generalized interictal EEG abnormalities and/or multiple areas of cerebral involvement should not automatically preclude epilepsy surgery in a child with intractable epilepsy and TSC.

The natural history of epilepsy in patients with TSC, tends from infancy into childhood to be one of increasing seizures frequency and severity, with poor response to antiepileptic drugs and a diminished quality of life because of the seizures and adverse medication effects. In late childhood and early adulthood this pattern may gradually change, often showing a spontaneous improvement in seizure frequency. However, some of the lesions (i.e., mesial frontal parasagittal tubers) are intrinsically epileptogenic and associated with very severe seizures. Unfavorable prognostic factors include onset earlier than 1 year of age, presence of several seizure types (infantile spasms and partial motor or complex partial seizure; drop attacks and atypical absences) multifocal discharges and/or SBS, and occurrence of new EEG foci during the evolution.

The choice of the proper antiepileptic drugs (AED) in children with TSC is an important decision, since a growing body of evidence shows that it may play a part in preventing future development of drug resistance. After the introduction of many new AEDs drug selection has become increasingly complex. The choice of AEDs should be based on the type of epileptic syndrome. However, diagnosis of the type of syndrome may be difficult at the onset in TSC children. Vigabatrin (VGB) has demonstrated efficacy in the treatment of infantile spasms, initially as add-on therapy and subsequently as monotherapy [1]. This drug appears to work rapidly, usually in 3–8 days after the onset of therapy. It is also appears to have considerably fewer and less severe side effects than conventional treatments. In our current practice VGB has replaced ACTH and sodium valproate as the first-choice treatment for infantile spasms in TSC. Lamotrigine (LTG) is emerging as more effective in generalized seizures, particularly atonic seizures and atypical absences, and in Lennox-Gastaut syndrome. Clinical data suggest that LTG is relatively nonsedative and that has positive effects on cognitive performances and behavior. Both VGB and LTG have demonstrated efficacy in partial seizures. In our experience VGB is effective mainly in partial epilepsies without secondary generalization and originating from occipital and posterotemporal regions [7]. By contrast, LTG is advisable in frontal lobe epilepsies with SBS. In cases of intractability a second monotherapy is recommended before polytherapy is considered. Some TSC patients may benefit from the use of a drug combination because the mechanisms of action is thought to be complementary. When complex partial seizures with SBS show clinical worsening during VGB treatment, the addition of LTG may lead to improvement of the seizures, alertness and school performance. In most patients with multifocal epilepsy or Lennox-Gastaut syndrome, total seizure control may be impossible. In these patients the aim of the treatment should be to suppress the more dangerous seizures (i.e., drop attacks that can cause head trauma) without producing unacceptable adverse effects. In our experience no patient requires more than two drugs, because seizure control is not significantly improved with add-on and there is an increased risk of side effects. Evaluation of behaviour and cognitive function is as important as the evaluation of seizure frequency in TSC. A decline in cognitive ability due to the persistence of intractable seizures should lead to prompt consideration of

epilepsy surgery. Clear localization of the most active epileptogenic focus and of the zone of the cortical abnormality may lead to tuberectomy and improved seizure control in selectively drug-resistant patients [2, 4].

Relationships between clinical and EEG findings and MRI

MRI has been reported to be more accurate than CT in detecting and localizing the tubers, which appear as high-intensity signal areas in T2-weighted images. Cortical tubers detected by MRI represent the epileptogenic foci of TSC, and a topographic relationship exists between EEG abnormalities and the largest MRI high-signal lesions [9]. MRI lesions in the occipital lobes show the best correlation with the EEG foci, whereas the weakest correlation is with frontal lesions. The age at seizure onset and the age when epileptiform activity becomes apparent on 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. SPECT and PET show that functional activity reflecting brain regional cortical maturation increases successively in different regions of the brain. Central, temporal and occipital cortex become progressively mature during the first months of life, whereas frontal cortex does not reach high functional levels until the second year of life. Therefore, it is not surprising that cortical lesions that are associated with infantile spasms are not epileptogenic later and that, in the same child, complex partial seizures originating from a more anterior tuber may not begin for a number of years. In TSC patients with intractable atonic seizures, there is a strong relationship between the presence of frontal tubers, focal spikes in the frontal or frontopolar areas and SBS, which is more likely to occur in frontal epilepsies than in other focal epilepsies. The presence of more than one focus in half of our patients suggests that SBS may also result from a complex interaction of multiple epileptogenic lesions. Patients with multiple lesions may have a greater tendency to show hypsarrhythmia at an early age, with subsequent development of multifocal slow spike-and-wave complexes.

However, it is well known that PET or SPECT may reveal hypometabolic or hypoperfused regions not predicted by MRI, demonstrating that the disturbance of cerebral function may be more extensive than indicated by morphologic imaging [25]. Hypometabolic areas on PET without any MRI correlate may be due to the presence of small tubers. Tubers have been shown ultrastructurally to have simplified synaptic patterns and therefore use less glucose than surrounding brain tissue. Recently, 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 CSF on conventional T2-weighted images [34]. These observations may explain why the correlation between MRI and EEG findings is not absolute.

An improvement in functional localization can be obtained by combining EEG and magnetoencephalography (MEG) signals. Whereas scalp EEG detects both tangential and radial sources, i.e., activity both in the sulci and in the gyri, MEG selectively measures tangential sources, i.e. activity in the sulci. Spatial resolution of MEG is about one-third better than that of EEG, because magnetic fields are not distorted by resistive properties of the skull and scalp. Combining MEG data on brain function with MRI data on brain structure, it is even possible to localize an equivalent dipole layer in a zone corresponding to a cortical tuber. A multimodal neurophysiological approach, including computerized EEG topography and magnetoencephalography, can give a better insight into the localization sources and classification of seizures associated with TSC, supporting the view that seizures are partial in most cases, clinical features depending on the localization of the cortical tubers.

Learning disabilities and mental retardation

Patients with TSC range from intellectually normal to severely retarded. The prevalence of learning disabilities varies from 38% to 80%, and when learning disability is present, 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. Recently, 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 [34]. Curatolo et al. [10] have suggested that both number and localization of cortical tubers play an important part 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 nonretarded individuals. All the patients with favorable 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 less severe epilepsy. They may have had different specific neuropsychological deficits related to the location of the cortical tubers, even when the epilepsy was in complete remission. By contrast, patients with stable mental retardation suffered from frequent partial seizures, developing multifocal or secondary generalized epilepsy, and were found on MRI to have multiple bilateral, strategically localized cortical tubers. Progressive mental deterioration observed in TSC children with intractable seizures may also be due to a heightened epileptogenicity of parasagittal frontal tubers. Recently, Shepherd et al. [32] reported that fewer tubers in the frontal regions might be a favorable predictor for mental development. In their series, TSC patients with infantile spasms had more tubers than those with other types of seizures, who in their turn had more tubers than those without seizures.

Behavioral problems

In addition to mental retardation, multiple behavioral problems, including sleep disorders, hyperactivity, attention deficit, aggressiveness, and autism, have been found in children with TSC [10, 17]. Sleep disorders, such as night waking, waking early, seizure-related sleep problems, and excessive daytime sleepiness, are considered one of the most common behavioral manifestations in children with TSC. In a study on 300 children investigated by postal questionnaire, Hunt and Stores [21] reported the presence of sleep problems in 58% of children and seizure-related sleep problems in 41%. Our findings [3] based on a polysomnographic study show a wide range of sleep abnormalities in children with TSC, similar to those reported in children with symptomatic partial epilepsy. The main perturbations that characterized the sleep organization of TSC patients were a reduced REM sleep, sleep instability, and fragmentation by frequent awakenings. Children with seizures show a more disrupted sleep architecture than seizure-free children. Therefore, sleep disorders seem to be mainly due to sleep-related epileptic events. Melatonin has recently been reported as effective in improving the disturbed sleep patterns of children with multiple neurologic handicaps [23]. TSC children suffering from hyperactivity and attention deficit disorder and showing a delayed sleep onset could benefit most.

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 TSC children reported as having autistic-type behavior had experienced infantile spasms and were mentally retarded, raising the question of cognitive defects as a primary cause of autism and behavior problems [8]. Although the pathogenesis of autism in individuals with seizures and mental retardation still remains a puzzle, it is possible that some of the behaviors exhibited by children with TSC are organically determined and 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 parieto-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 [10]. An alternative explanation is that this typical pattern of abnormal behavior seen in TSC, including aggresiveness, irritability, stereotypy, and autistic behavior, reflects more direct effects of an abnormal genetic program. If so, then TSC appears as a dramatic linkage between a gene disorder and discrete behavioral abnormalities. This opens a path for the study and treatment of biological bases of behavior, a current focus of neurosciences. The identification of genes causing TSC will help us to improve the definition of timing and anatomic localization, including both regional and cellular distribution of *TSC* gene expression and subcellular localizations of the TSC1 and TSC2 protein products and their contribution to behavior. When the biochemical abnormalities are better understood, a rational approach to pharmacotherapy directed at the specific underlying neurotransmitter systems may finally be developed.

Hydrocephalus and subependymal giant cell astrocytomas

Hydrocephalus and brain tumors are two specific neurosurgical complications of TSC. Blockage of, usually, one foramen of Monro or, more rarely, the acqueduct by a subependymal or intraventricular nodule or tuber localized in these areas may result in obstructive hydrocephalus and in symptoms of increased intracranial pressure. Another complications is the neoplastic transformation of a previous benign nodule into a giant cell astrocytoma. Subependymal giant cell astrocytomas occur in 6–14% of TSC patients, who present either with a worsening of epileptic manifestations or with symptoms of intracranial hypertension [31]. Early identification of a giant cell astrocytoma enables it to be removed before symptoms arise. Our patients have routine CT or MRI yearly. Those with a small tumor can be followed up with more frequent MRI (every 3–6 months), but any evidence of progressive enlargement in size should prompt surgery. Lesions usually, but not always, show arrest of growth in late adolescence. Partial calcification of the lesion may be a good prognostic indicator.

Concluding remarks

One of the most significant advances in the last few years in the clinical study of localization-related symptomatic epi-

lepsies has been the search for topographic correlations between seizure type and the epileptogenic zone. Prompt detection and precise localization of lesions may lead to surgical treatment and improved seizure control. Correlation between cortical tubers detectetd by MRI and epileptogenic areas is far from being definitive in TSC. One problem is that the subtle focal onset of secondarily generalized seizures may not be recognized, and seizures may be incorrectly diagnosed as generalized from the onset. The risk for incorrect diagnosis is high in seizure types that are by definition generalized, such as infantile spasms, atypical absences, and atonic seizures. In these cases accurate topographic localization of epileptogenic foci by visual inspection of the tracing may be difficult when apparently bilaterally synchronous EEG abnormalities occur. Spike mapping of the EEG may allow prompt recognition of the focal onset of apparently generalized bursts, revealing small interchannel time differences. Identification of dipole sources of interictal spikes prove to be more accurate both in time and in space than visual inspection of EEG tracings. The combined use of topographic mapping of EEG and dipole localization methods may provide important clues to the localization of the epileptogenic areas, even in cases with apparently synchronous spike-and-wave bursts, showing that such patients may be candidates for epilepsy surgery. In the future, mapping the results on a three-dimensional MRI reconstruction will allow more accurate localization of the zone of the cortical focal abnormalities and help the surgeon to perform individualized and conservative resections in children with intractable seizures associated with TSC.

References

1. Aicardi J (1995) European experience with use of vigabatrin as first-line monotherapy in infantile spasms (abstract). Epilepsia 36:S102
2. Bebin EM, Kelly PJ, Gomez MR (1993) Surgical treatment for epilepsy in cerebral tuberous sclerosis. Epilepsia 34:651–657
3. Bruni O, Cortesi F, Giannotti F, Curatolo P (1995) Sleep disorders in tuberous sclerosis: a polysomnographic study. Brain Dev 17:52–56
4. Bye AM, Matheson JM, Tobias VH, Mackenzie RA (1989) Selective epilepsy surgery in tuberous sclerosis. Aust Pediatr J 25:243–245
5. Carbonara C, Longa L, Grosso E, Borrone C, Garre MG, Brisigotti M, Migone N (1994) 9q34 loss of heterozygosity in a tuberous sclerosis astrocytoma suggests a growth suppressor-like activity also for the TSC1 gene. Hum Mol Genet 3:1829–1831
6. Chiron C, Raynaud G, Cusmai R, Dulac O, Plouin P (1990) Morphological functional study in tuberous sclerosis: brain MRI/SPECT correlations (abstract). Epilepsia 31:613
7. Curatolo P (1994) Vigabatrin for refractory partial seizures in children with tuberous sclerosis. Neuropediatrics 25:55
8. Curatolo P, Cusmai R (1987) Autism and infantile spasms in children with tuberous sclerosis. Dev Med Child Neurol 29:550–551
9. Curatolo P, Cusmai R (1988) MRI in Bourneville disease: relationships with EEG findings. Neurophysiol Clin 18:149–157
10. Curatolo P, Cusmai R, Cortesi F, Jambaqué I, Chiron C, Dulac O (1991) Neurologic and psychiatric aspects of tuberous sclerosis. Ann NY Acad Sci 615:8–16
11. Curatolo P, Seri S, Cerquiglini A (1993) Topographic spike mapping of EEG in tuberous sclerosis (abstract). Neuropediatrics 24:178
12. Cusmai R, Chiron C, Curatolo P, Dulac O, Tran Dinh S (1990) Topographic comparative study of MRI and EEG in 34 children with tuberous sclerosis. Epilepsia 31:747–755
13. Erba G, Duchowny M (1990) Partial epilepsy and tuberous sclerosis: indications for surgery in disseminated disease. J Epilepsy 3:315–319
14. European Chromosome 16 Tuberous Sclerosis Consortium (1993) Identification and characterization of the tuberous sclerosis gene on chromosome 16. Cell 75:1–11
15. Fryer AE, Connor JM, Povey S, Yates JRW, Chalmers A, Osborne JP (1987) Evidence that the gene for tuberous sclerosis is on chromosome 9. Lancet I:659–661
16. Gastaut H, Zifkin B, Magaudda A, Mariani E (1987) Symptomatic partial epilepsies with secondary bilateral synchrony: differentiation from symptomatic generalized epilepsies of the Lennox-Gastaut type. In: Wieser HG, Elger CE (eds) Presurgical evaluation of epilepsies. Springer, Berlin Heidelberg New York, pp308–316
17. Gillberg IC, Gillberg C, Ahlsen G (1994) Autistic behaviour and attention deficits in tuberous sclerosis: a population-based study. Dev Med Child Neurol 36:50–56
18. Gomez MR (1988) Neurologic and psychiatric features. In: Gomez MR (ed) Tuberous sclerosis. Raven Press, New York, pp 21–36
19. Gomez MR (1991) Phenotypes of the tuberous sclerosis complex with a revision on diagnostic criteria. Ann NY Acad Sci 615:1–7
20. Hirose T, Scheithauer BW, Lopes MBS (1995) Tuber and subependymal giant cell astrocytoma associated with tuberous sclerosis: an immunohistochemical, ultrastructural, and immunoelectron microscopic study. Acta Neuropathol 90:387–399
21. Hunt A, Stores G (1994) Sleep disorders and epilepsy in children with tuberous sclerosis: a questionnaire based study. Dev Med Child Neurol 36:108–115
22. Huttenlocher PR, Wollman RL (1991) Cellular neuropathology of tuberous sclerosis. Ann NY Acad Sci 615:140–148
23. Jan JE, Espezel H, Appleton RE (1994) The treatment of sleep disorders with melatonin. Dev Med Child Neurol 36:97–107
24. Kandt RS, Haines JL, Smith M (1992) Linkage of an important gene locus for tuberous sclerosis to a chromosome 16 marker for polycystic kidney disease. Nat Genet 2:37–41
25. Nixon JR, Miller GM, Gomez MR (1989) Cerebral tuberous sclerosis: postmortem MRI and pathology anatomy. Mayo Clin Proc 64:305–3111
26. Osborne JP, Fryer A, Webb D (1991) Epidemiology of tuberous sclerosis. Ann NY Acad Sci 615:125–127

27. Povey S, Burley MW, Attwood J (1994) Two loci for tuberous sclerosis: one on 9q34 and one on.16p13. Ann Hum Genet 58:107–127
28. Roach ES, Smith M, Huttenlocher P, Bhat M, Alcorn D, Hawley L (1992) Report of the diagnostic criteria comittee of the National Tuberous Sclerosis Association. J Child Neurol 7:221–224
29. Sampson JR, Harris PC (1994) The molecular genetics of tuberous sclerosis. Hum Mol Genet 3:1477–1480
30. Seri S, Cerquiglini A, Cusmai R, Curatolo P (1991) Tuberous sclerosis: relationship between topographic mapping of EEG, VEPs and MRI findings. Neurophysiol Clin 21:161–172
31. Shepherd CW, Scheithauer BW, Gomez MR, Altermatt HJ, Katzmann JA (1991) Subependymal giant cell astrocytoma: a clinical, pathologic, and flow cytometric study. Neurosurgery 38:864–868
32. Shepherd CW, Houser OW, Gomez MR (1995) MR findings in tuberous slcerosis complex and correlation with seizure development and mental impairment. AJNR Am J Neuroradiol 16:149–155
33. Szelies B, Herholz K, Heiss D (1983) Hypometabolic cortical lesions in tuberous sclerosis with epilepsy: demonstration by PET. J Comput Assist Tomogr 7:946–953
34. Takanashi J, Sugita K, Fujii K, Niimi H (1995) MR evaluation of tuberous sclerosis: increased sensitivity with fluid-attenuated inversion recovery and relation to severity of seizures and mental retardation. AJNR Am J Neuroradiol 16:1923–1928