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 2801
Fax: (39) 6-59 17415
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 consists 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-