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Ictal signs in tuberous sclerosis complex: Clinical and video-EEG features in a large series of recorded seizures

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ABSTRACT

Epilepsy is the most common neurological symptom in tuberous sclerosis complex (TSC), occurring in 72–85% of affected individuals. Despite the large number of patients reported, their electroclinical phenotype has been rarely described. We analyzed seizure semiology through ictal video-electroencephalography (V-EEG) recordings in a large series of patients. In this multicenter study, we reviewed V-EEGs of 51 patients: ictal recordings were analyzed in correlation with their clinical variables.

The median age of epilepsy onset was six months (one day–16 years), with onset in the first year of life in 71% patients (36/51), in 10 of them during the neonatal period. Sixty-five percent of patients (33/51) experienced epileptic spasms in their life, with late-onset (>two years) in five; 42% of the epileptic spasms persisted after age two years, despite the onset in the first year of life.

We identified four different electroclinical subsets: focal epilepsy (35%, 18/51), Lennox–Gastaut Syndrome evolution (27%, 14/51), focal seizures with persisting spasms (33%, 17/51), and spasms only (4%, 2/51).

We reviewed 45 focal seizures, 13 clusters of epileptic spasms, and seven generalized seizures. In 12 patients, we recorded different seizure types. In 71% of the focal seizures (32/45), the ictal pattern was focal without diffusion. In 38% of the patients (5/13) epileptic spasms were related to typical diffuse slow wave pattern associated with superimposed fast activity, with focal predominance.

Focal seizures and focal spasms resulted as the most frequent seizure types in TSC. Seizure onset was variable but showing a predominant involvement of the frontocentral regions (40%). Discrete clinical signs characterized the seizures, and behavioral arrest was the predominant first clinical objective sign. Epileptic spasms were a typical presentation at all ages, frequently asymmetrical and associated with lateralizing features, especially in older patients.

1. Introduction

Tuberous sclerosis complex (TSC) is an autosomal-dominant multisystemic disorder with high clinical variability. It is caused by mutations in either *TSC1* (Chr. 9) or *TSC2* (Chr. 16), which encode Hamartin and Tuberin, respectively [1]. The prevalence is approximately 1:20,000, with an incidence of 1:6000 live births. The hallmark of the disease is the development of hamartomatous lesions affecting brain, skin, kidneys, eyes, heart, and lungs. The central nervous system (CNS) is affected in 90% of the individuals: the pathological CNS lesions consist in cortical tubers, white matter radial migration lines, subependymal nodules (SENs), and subependymal giant cell astrocytomas (SEGA) [1,2].

The protein products of *TSC1* and *TSC2*, together with TBC1D7, form a trimeric complex that physiologically inhibits the mammalian target of rapamycin (mTOR) signaling cascade. Pathogenic variants in *TSC1* or *TSC2* cause hyperactivation of mTOR, which leads very early to an alteration in cellular morphology, synaptogenesis, and imbalance between excitation and inhibition, providing substrate for epilepsy, but also for many other neurodevelopmental disorders, renamed as TSC-associated neuropsychiatric disorders (TAND) [3].

Epilepsy is the most common neurological symptom occurring in 72–85% of affected individuals, beginning in the first three years of life in 80% of the patients (particularly in the first year of life, 67%), although

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an onset in adulthood is also possible. Early onset epilepsy usually presents with focal seizures or infantile spasms, but all seizure types have been clinically described [4,5].

Multiple seizure types often characterize the evolution, and one third of the patients experience a progression to Lennox–Gastaut Syndrome (LGS). Drug-resistant epilepsy is common in TSC (2/3 of the patients), and is related – together with early onset – to poor developmental outcome [5]. In particular, infantile spasms are often associated with severe neurocognitive impairment and poor neurological prognosis, with a high prevalence in children with TSC [3].

By reviewing the literature, we found that the electroclinical phenotype associated with epilepsy in patients with TSC has been rarely described. Moreover, most studies consider clinical data instead of ictal recordings, with a possible overestimation of generalized seizures [4–8].

We hypothesized the following: 1. Recorded seizures in TSC may sometimes differ from the reported description of ictal events; 2. If so, recognizing the actual electroclinical pattern may direct management and therapeutic choices. Therefore, the aim of this study was to describe the electro-clinical features of video-electroencephalography (V-EEG) recorded seizures in a large population with TSC, in order to evidence distinctive characteristics that could allow earlier treatment with possible impact on the patients' long-term prognosis.

2. Materials and methods

2.1. Patients

We performed a multicenter retrospective study including 51 patients with a definite diagnosis of TSC and V-EEG documented seizures, followed at the Epilepsy Center—Child Neuropsychiatric Unit, Tuberous Sclerosis Clinic, ASST Santi Paolo e Carlo (25 subjects), "C. Munari" Epilepsy Surgery Center at Niguarda Hospital (23 subjects), and the Pediatric Neurology Unit at "V. Buzzi" Hospital (3 subjects).

2.2. Data collection and methods

We collected clinical information about gender, date of birth, family history (TSC and epilepsy diagnosis in family members), age at TSC diagnosis, age at follow-up, and genetic results for the detection of *TSC1*/*TSC2* point mutations and deletions.

We also considered seizure type and age at onset, electroclinical evolution, presence of epileptic spasms, febrile seizures and status epilepticus, seizure frequency, antiepileptic drugs (AEDs), history of drug-resistance, presurgical evaluation and surgical resection, vagus nerve stimulation, and therapy with mTOR inhibitors (Everolimus).

We reviewed the brain magnetic resonance imaging (MRI) studies, to determine number and location of the cortical lesions, SENs, and SEGA [9,10].

Developmental status (total Developmental Quotient, DQ) or cognitive level (total Intelligence Quotient, IQ) was assessed through standardized scales (Griffiths' Scales of Infant Development, GMDS-ER, Wechsler Preschool and Primary Scales of Intelligence, WPPSI).

Scalp EEGs with synchronized videos, applying the International 10–20 System of electrode placement, were recorded directly or by cable telemetry with more than 16 channels (except for the neonatal period, in which 12 channels are used according to the International 10–20 system) and at least three polygraphic channels (electrocardiogram and deltoid muscles). We examined the electroclinical features of all recorded seizures. Semiological seizure analysis classification was based on the International League Against Epilepsy (ILAE) classification (2017). A more detailed description of symptoms and signs was performed using the ILAE glossary, when the early age of the patients and the developmental delay did not allow a proper definition of seizures [11].

For each patient, at least one seizure was recorded; we analyzed the electroclinical features of the seizures with better characterization based on Authors' agreement. Subjective manifestations, initial/leading objective ictal clinical signs, and evolution were taken into account.

We transferred the clinical, EEG, and genetic data into an electronic database and analyzed them using the Statistical Package for the Social Sciences (SPSS, IBM, Chicago, IL, U.S.A.) for Macintosh, version 24.0. We divided the patients into three groups according to the location of the epileptogenic foci (frontal [F]/frontocentral [FC]/frontocentrotemporal [FCT] vs temporal [T]/centroparietotemporal [CPT] vs temporooccipital [TO]/occipital [O]). We compared the age at recording using one-way analysis of variance (ANOVA) with Bonferroni post hoc. We considered a two-tailed p value of 0.05 or less statistically significant.

Ethics committee approval for the study was obtained.

3. Results

3.1. Population characteristics

Fifty-one patients (22 F, 29 M) affected by TSC were included in this study.

Six individuals had a positive family history of TSC. Mutational analysis was available in 34 patients (12 *TSC1*, 22 *TSC2*).

The mean age at TSC diagnosis was three years (range: 0–33 years); 24% (12/51) of our patients had a diagnosis in the prenatal period, because of cardiac rhabdomyomas detected by prenatal ultrasound. Epilepsy was the reason for diagnosis in 35% (18/51). In the other patients, other clinical signs suggested the diagnosis of TSC. The prevalence of intellectual disability (ID) was 65% (33/51). Behavioral disturbances were reported by caregivers in 57% (29/51) of the patients.

Data regarding epilepsy, EEG, and MRI features are summarized in Table 1.

Median age at epilepsy onset was six months (range: one day–16 years); 71% (36/51) had epilepsy onset in the first year of life.

Table 1
Epilepsy characteristics, EEG, and MRI features.

	Total n. 51	%
Epilepsy onset		
<1 month	10	20
1–11 month	26	51
1–2 year	10	20
3–9 year	2	4
10–15 year	1	1
16 year and older	2	4
Seizure at onset		
Focal	30	59
Spasms	21	41
History of spasms	33	65
Febrile seizures	10	20
SE	7	14
>1 seizure type	32	63
Daily seizures	37	72
Interictal EEG		
Focal	17	33
Multifocal	19	37
Diffused + focal	11	21
Diffused	4	8
Hypsarrhythmia	3	6
MRI		
Cortical tubers	51	100
<5	7	14
5–10	4	8
>10	40	78
Bilateral	50	98
SENs	39	76
SEGA	10	20

SE: status epilepticus; MRI: magnetic resonance imaging; SENs: subependymal nodules; SEGA: subependymal giant cell astrocytomas.