



## Influence of seizures on early development in tuberous sclerosis complex



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### ABSTRACT

**Objective:** Epilepsy is commonly seen in Tuberous Sclerosis Complex (TSC). The relationship between seizures and developmental outcomes has been reported, but few studies have examined this relationship in a prospective, longitudinal manner. The objective of the study was to evaluate the relationship between seizures and early development in TSC.

**Methods:** Analysis of 130 patients ages 0–36 months with TSC participating in the TSC Autism Center of Excellence Network, a large multicenter, prospective observational study evaluating biomarkers predictive of autism spectrum disorder (ASD), was performed. Infants were evaluated longitudinally with standardized evaluations, including cognitive, adaptive, and autism-specific measures. Seizure history was collected continuously throughout, including seizure type and frequency.

**Results:** Data were analyzed at 6, 12, 18, and 24 months of age. Patients without a history of seizures performed better on all developmental assessments at all time points compared to patients with a history of seizures and exhibited normal development at 24 months. Patients with a history of seizures not only performed worse, but developmental progress lagged behind the group without seizures. All patients with a history of infantile spasms performed worse on all developmental assessments at 12, 18, and 24 months. Higher seizure frequency correlated with poorer outcomes on developmental testing at all time points, but particularly at 12 months and beyond. Patients with higher seizure frequency during infancy continued to perform worse developmentally through 24 months. A logistic model looking at the individual impact of infantile spasms, seizure frequency, and age of seizure onset as predictors of developmental delay revealed that age of seizure onset was the most important factor in determining developmental outcome.

**Conclusions:** Results of this study further define the relationship between seizures and developmental outcomes in young children with TSC. Early seizure onset in infants with TSC negatively impacts very early neurodevelopment, which persists through 24 months of age.

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### 1. Introduction

Tuberous Sclerosis Complex (TSC) is a genetic disorder that affects multiple organ systems and is present in approximately 1 in 6000 individuals [1]. Neurologic manifestations are the most common with epilepsy affecting approximately 80% of individuals, two-thirds of whom begin developing epilepsy in the first year

of life [2]. Neurodevelopmental disorders, including intellectual disability, autism spectrum disorder (ASD), and behavioral difficulties, also are highly prevalent, affecting about 50% of individuals with TSC [3–5].

The association between early age at seizure onset and poor neurodevelopmental outcome has been consistently reported [6,7]. Type and severity of seizures, especially infantile spasms, along with early age of seizure onset also appear to be associated with increased likelihood of cognitive and behavioral difficulties, particularly if seizures are not controlled [8–12]. Similar associations have been reported for higher risk for ASD in TSC [9,13–15], and it has been suggested that epilepsy may be an independent predictor of intellectual

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ability in TSC [7,10,16]. At this time, it is unclear as to whether neurodevelopmental disorders are caused by the underlying brain abnormalities seen in TSC, subsequent development of epilepsy, or both [17]. Few studies have looked at the relationship between seizures and developmental and behavioral outcomes in a prospective, longitudinal manner and most studies lack detailed phenotypic characterization of development in the earliest years of life, when seizures and epilepsy first emerge.

By evaluating the temporal relationship between epilepsy onset and developmental functioning before and after seizures first emerge, our aim was to better define the association between neurodevelopmental outcome and epilepsy in infants and toddlers diagnosed with TSC. Here we report analysis of 130 patients ages 0–36 months with TSC participating in the TSC Autism Center of Excellence Network (TACERN), a large multicenter, prospective observational study to identify clinical, structural, and electrophysiological biomarkers predictive of ASD. Through serial developmental assessments and continuous seizure reporting, we are able to report in-depth characterization and temporal evolution of the developmental profile of infants with TSC over the first two years of life and explore the real-time impact of seizures during this critical phase of neurodevelopment.

## 2. Methods

### 2.1. Subject recruitment

Infants with TSC were enrolled into TACERN ([clinicaltrials.gov](http://clinicaltrials.gov), NCT 01780441) at one of five sites across the United States (Cincinnati Children's Hospital Medical Center, Boston Children's Hospital, University of Alabama at Birmingham, University of California at Los Angeles, and McGovern Medical School at the University of Texas Health Science Center at Houston). An IRB approval was obtained at each of the five sites, and informed consent was acquired from all participating families prior to enrollment.

Inclusion criteria for the study consisted of the following: 1) age 3–12 months at time of enrollment; 2) meets clinical or genetic criteria for definitive diagnosis of TSC [18]. Patients were excluded if: 1) gestational age was <36 weeks at the time of delivery with significant perinatal complications (i.e. respiratory support, confirmed infection, intraventricular hemorrhage, cardiac compromise); 2) they had taken an investigational drug as part of another research study within 30 days prior to study enrollment; 3) were taking an mTOR inhibitor (rapamycin, sirolimus, or everolimus) orally at the time of study enrollment; 4) had a Subependymal Giant Cell Astrocytoma (SEGA) requiring medical or surgical treatment; 5) had a history of epilepsy surgery; 6) or had any contraindications to MRI scanning.

### 2.2. Study design

All TACERN subjects were evaluated longitudinally at ages 3, 6, 9, 12, 18, 24 and 36 months. At each age, children underwent standardized evaluations, using developmental and adaptive measures. Clinical data were collected at enrollment and at each subsequent time point including basic demographics, medical and family history, participation in therapies (including type and frequency), past and current seizure history (using patient diaries collected and reviewed at every visit, as described in additional detail below), concomitant medications, and medical co-morbidities to determine if specific clinical factors modify the course of development. A physical examination from which clinical findings was performed at each visit. Although not the focus of the current analysis, EEG and MRI also were obtained at scheduled intervals as part of the TACERN study. A yearly calibration meeting was held to ensure developmental assessment reliability across all sites for the entire study period.

### 2.3. Developmental and behavioral assessments

Developmental assessments at each visit were carried out by a licensed psychologist and/or speech therapist blinded to each patient's clinical and seizure history at the time of testing and who had obtained research reliability on diagnostic (e.g., ADI-R and ADOS-2) and experimental (e.g., AOSI, ESCS) measures included in this project. All personnel were certified as being research-reliable on these measures. Developmental functioning at each visit was assessed using the Mullen Scales of Early Learning (MSEL) [19]. The MSEL consists of five domains (gross motor, fine motor, expressive language, receptive language, and visual reception) and also provides an overall composite score. Adaptive functioning was assessed using the Vineland Adaptive Behavior Scales, 2nd Edition, Survey Interview (VABS) and was completed at 6, 12, 18, 24, and 36 months [20]. The VABS is a caregiver-interview that assesses social, communication, motor, and daily living skills. The Preschool Language Scale-5th Edition (PLS-5) was completed at all visits [21]. This is an interactive, play-based assessment that provides information about receptive and expressive language skills for children from birth through age 7 years. Other assessments were performed including the Early Social Communication Scales (ESCS) and Child Behavior Checklist (CBCL), but results were not available for inclusion in the current analysis. At 12 months of age, assessment for autism risk was performed using the Autism Observation Scale for Infants (AOSI) [22]. The AOSI is a tool that looks at specific behavioral risk markers for ASD. At ages 24 and 36 months, formal assessment for autism using the Autism Diagnostic Observation Schedule-2 (ADOS-2) was performed [23], as well as the Autism Diagnostic Interview-Revised (ADI-R) [24]. The ADOS is a semi-structured, interactive observation tool used to assess for ASD. The ADI-R is a parent interview that focuses on a child's developmental history, current functioning, social skills, communication and behaviors, and interests. The current analysis focuses on assessments through 24 months of age, since the majority of TACERN subjects had not completed the 36-month visit at the time of data cut-off.

### 2.4. Determination of seizure onset and seizure frequency

A detailed seizure history was obtained from the patients via a seizure diary. Seizure diaries were given to the parent/guardian to record type and frequency of seizures. At enrollment, parents were shown a seizure recognition educational DVD to improve seizure identification and accurate reporting. From the diaries, seizures (i.e. focal, generalized, infantile spasms) were classified by the site neurologist using ILAE criteria [25]. In the present analysis, seizure onset was defined as the first recorded clinical seizure of any type recorded in the seizure diary. To capture the overall seizure frequency in association with the time of each developmental assessment, the total number of seizures during the six-month period (please see below for further detail regarding data analysis) in between assessments was used to obtain an average number of seizures per month. Because of significant variability among subjects with outliers at the highest end (range 0–981 seizures per month), seizure frequency was also grouped into seizure severity categories for additional analyses as follows): Category 1 (no seizures), Category 2 (1 to 30 seizures, corresponding to an average of less than one seizure daily), Category 3 (31 to 60 seizures, corresponding to an average of one seizure daily), and Category 4 (greater than 60 seizures, corresponding to an average of multiple seizures daily). Of note, seizure management at each site was determined by the treating neurologist following best clinical practices [26].

### 2.5. Statistical analysis

Assessments performed at 6, 12, 18, and 24 months were used for analysis. An Early Learning Composite standard score from the MSEL was used to determine overall developmental functioning, with a score <70 used to define developmental delay. In some cases the Early

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