



Published in final edited form as:

Epilepsy Behav. ; : 106844. doi:10.1016/j.yebeh.2019.106844.

Language Predictors of Autism Spectrum Disorder in Young Children with Tuberous Sclerosis Complex

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Abstract

Background: Epilepsy has previously been implicated in the development of autism spectrum disorder (ASD) in the setting of Tuberous Sclerosis Complex (TSC). However, the role of language in this relationship is unclear, and the specific relationship between ASD, epilepsy, and language development in this population has not been well-studied.

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Objectives: Identify the role of early language in subsequent development of ASD, evaluate the impact of epilepsy as a covariate on language development, and evaluate the relationship between epilepsy, language development, and development of ASD.

Methods: This study included 154 children ages 3-36 months with TSC who were enrolled in the TSC Autism Center of Excellence Research Network (TACERN), a multicenter, prospective observational study to identify biomarkers of ASD. Developmental and autism-specific assessments were administered longitudinally. Appropriate variables from the Mullen Scales of Early Learning (MSEL), Vineland Adaptive Behavior Scales, 2nd Edition (VABS-II), and Preschool Language Scales, 5th Edition (PLS-5) were used to assess patients' language skills. At 36 months clinical best estimate, which was based on clinical assessment and observation, was used to determine a diagnosis of ASD.

Results: By 12 months, all language variables on the MSEL, PLS-5, and VABS-II significantly predicted an ASD diagnosis at 36 months. Age at seizure onset was associated with language scores in that later seizure onset was associated with improved language scores on the MSEL, VABS-II, and PLS-5. Seizure onset prior to 6 months was associated with a diagnosis of ASD at 36 months. Higher seizure frequency negatively correlated with language scores at 12 months and beyond. Higher seizure frequency was also associated with an ASD diagnosis at 36 months. When looking at the relationship between epilepsy, language, and ASD diagnosis, by 18 months language scores were more associated with a later ASD diagnosis at 36 months compared to age at seizure onset, which was a better predictor of later ASD diagnosis earlier in development.

Conclusion: Analysis of language variables and epilepsy characteristics from 6-36 months and ASD diagnosis at 36 months revealed significant relationships between all three variables. While the direction of these relationships needs further research, epilepsy, language, and the development of ASD are integrally related in young children with TSC.

Keywords

Autism Spectrum Disorder; Tuberous Sclerosis Complex; Language; Development; Seizures

1.1 Introduction

Tuberous Sclerosis Complex (TSC) is a rare neurocutaneous disorder with an incidence ranging between approximately 1:6,760 and 1:13,520 live births each year[1]. Individuals with TSC exhibit high rates of developmental delay and intellectual disability with rates ranging from 45-70% with a bi-modal distribution[2-4]. Within the TSC population, approximately 40-50% of patients are diagnosed with autism spectrum disorder (ASD)[5-8], compared to idiopathic ASD, which affects between 1-2% of the general population[9].

Additionally, approximately 70-80% of individuals with TSC develop epilepsy at some point in their lives, most commonly within the first 3 years[10, 11]. Early age at seizure onset has been associated with deficits in development and cognition[4, 10, 12]. A prospective study by Bolton and colleagues assessed genetic, neurological and epilepsy-related factors and found that a higher seizure burden was associated with worse cognitive outcome[13]. This same study also found that tuber load, history of status epilepticus, and genetic mutation for

TSC also contributed to overall cognition. Studies have also repeatedly implicated epilepsy as a factor in the development of ASD in individuals with TSC[14, 15].

Studies looking at younger siblings of individuals with ASD have shown an increased incidence of language delays in those who eventually go on to be diagnosed with ASD[16, 17]. In addition, prospective, longitudinal studies have shown that infants with TSC who eventually go on to get diagnosed with ASD exhibit delays in non-verbal abilities, including visual reception and fine motor skills, as early as 6 months and across all developmental domains by 9 months[7]. While seizure onset and frequency have been linked to worse developmental outcomes in TSC, studies have not yet evaluated the potential role of language development, specifically, in this relationship. Furthermore, both epilepsy and language delay have been associated with a greater incidence of ASD; therefore, it is worthwhile investigating each separately and combined as potential predictors of a future diagnosis of ASD in infants and toddlers with TSC who are at increased risk for language delay, epilepsy, and ASD. Because TSC results from a genetic mutation and can be diagnosed prenatally or at birth, it provides us with a unique opportunity to study early language development, ASD and epilepsy.

The characteristics of communication, in terms of both verbal and nonverbal communication, are important when considering ASD. Although there are individuals with high-functioning ASD who have somewhat “preserved” overall language function, they exhibit other communication deficits. These deficits manifest themselves as pragmatic language deficits, e.g., using very pedantic language, and/or very socially inappropriate language. Furthermore, language deficits of any kind (even mild) translate to very significant issues later in life. It is still unclear which assessment measures and at what ages communication, particularly language, be reliably used to stratify children into risk groups for future ASD diagnosis. In addition, individuals with TSC are at high risk for both communication deficits and ASD. Thus, the purpose of this investigation is to determine the role that language development plays in predicting which children later get diagnosed with ASD. We also investigate how comorbid seizures, which are common in this population, affect the relationship between language development and ASD.

1.2 Methods

1.2.1 Subject Recruitment

This analysis is a part of a larger set of studies within the TSC Autism Center of Excellence Research Network (TACERN), a consortium of five hospital programs throughout the country that was established in 2012 (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)[18]. TACERN is a multi-center, prospective observational study that utilizes serial clinical, structural, and electrophysiological assessments in early life to identify biomarkers and probe underlying relationships and pathophysiology of ASD in TSC ([clinical trials.gov](https://clinicaltrials.gov),). IRB approval was obtained at eachw of the five sites, and informed consent was acquired from all participating families prior to enrollment.

Children were included in the study if they were between the ages of 3 and 12 months at enrollment and met clinical or genetic criteria for definitive diagnosis of TSC[19]. Exclusion criteria included gestational age < 36 weeks at time of delivery with associated significant perinatal complications (i.e. respiratory support, confirmed infection, intraventricular hemorrhage, cardiac compromise) or history prior to enrollment of treatment with an oral mTOR inhibitor (sirolimus, everolimus), presence of sub-ependymal giant cell astrocytoma (SEGA) requiring medical or surgical treatment, or epilepsy surgery.

1.2.2 Study Design

Basic demographics, medical and family history, baseline and interval developmental history, participation in non-pharmacologic interventional therapies, seizure history (including seizure onset, type, and frequency), concomitant medications, and medical comorbidities also were collected throughout the study. A physical examination from which clinical findings were recorded was performed at each visit. EEG and MRI obtained at scheduled intervals as part of the TACERN study were not included in the current analysis.

Longitudinal developmental assessments were performed at ages 3, 6, 9, 12, 18, 24 and 36 months, along with ASD-specific assessments at 12, 24, and 36 months of age. A yearly calibration meeting was held to ensure developmental assessment reliability across all sites for the entire study period. The comprehensive battery included the Mullen Scales of Early Learning (MSEL), Vineland Adaptive Behavioral Scales, 2nd edition (VABS-II), Preschool Language Scales, 5th edition (PLS-5), Child Behavior Checklist (CBCL), Early Social Communication Scale (ESCS), Autism Diagnostic Observation Schedule, 2nd edition (ADOS-2), Autism Diagnostic Interview-Revised (ADI-R), and Autism Observation Scale for Infants (AOSI). The MSEL was administered at each visit and is a clinician-based assessment used to assess developmental function[20]. Developmental quotients (DQ) were calculated for the five separate subdomains (Gross Motor, Fine Motor, Visual Reception, Expressive Language, and Receptive Language). An Early Learning Composite Score was reported as a standard score and encompasses all of the subdomains with exception of gross motor. The VABS-II, a parent report tool, was used to rate communication, daily living skills, motor skills, and socialization[21]. The PLS-5 is a combined parent report/clinical observation tool that assesses total language, auditory comprehension, and expressive communication[22]. All three assessment tools were administered at 6, 9, 12, 18, 24, and 36 months, with the exception of the VABS-II, which was not administered at 9 months.

A clinical diagnosis of ASD was based on clinical best estimate, which encompassed objective assessments (ADOS-2, ADI-R) and the clinician's impression of the patient's overall clinical status (includes developmental functioning and impact of seizures).

A detailed seizure history was obtained from the participants 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[23]. Seizure type, date of onset for each seizure type, and frequency of each seizure type was recorded. In the present analysis, seizure onset was defined as the first recorded clinical seizure of any

type recorded in the seizure diary. Seizure frequency was calculated by dividing the total number of seizures over a 6-month time frame (the time between developmental assessments), and an average seizure frequency per month was calculated.

1.2.3 Statistical Analysis

ASD diagnosis was used as the primary outcome measure, and children were grouped as to having or not having a diagnosis of ASD at 36 months.

Variables specific to language in the MSEL and VABS, as well as all of the variables from the PLS-5, were used to determine association between language development and ASD diagnosis. Language variables for the MSEL included the expressive language age equivalent and receptive language age equivalent. Language variables for the VABS-II included communication domain standard score, expressive language subdomain age equivalent, and receptive language subdomain age equivalent. For the PLS-5, scores for expressive communication, auditory comprehension, and total language were reported as standard scores and age equivalents due to the assessment having a floor of 50, which may fail to capture lower functioning individuals. Standard scores on the Early Learning Composite on the MSEL and Adaptive Behavior Composite on the VABS-II were used as measures of overall developmental functioning. Age equivalents were converted into developmental quotients.

Summary statistics including means, standard deviations, and percentages, as appropriate, were derived for demographic variables. Spearman correlation coefficients, along with their p-values (versus zero), were derived for seizure frequency with each of the MSEL, PLS-5, and VABS-II scores. While MSEL and VABS scores were normally distributed, Spearman was used to examine seizure burden relationship with language scores because seizure burden was not normally distributed. Univariate logistic regression models were conducted with the dichotomous outcome ASD diagnosis and the independent variable was one of the MSEL, VABS-II, or PLS-5 measures. The odds ratios, with 95% confidence intervals, and p-values were derived for each measurement separately for each visit. Further, multivariate logistic models were conducted in these cases for patients diagnosed with epilepsy adjusting for age at seizure onset. (Note that repeated measures analyses was not conducted because we were primarily interested in test results at specific ages and their effect on the single ASD outcome). Fisher's Exact tests were conducted for each of these variables and ASD diagnostic outcome at 36 months. Longitudinal analyses were conducted where the responses were the different language variables as a function of age of seizure onset. Lastly, a survival analysis model was examined with age of seizure onset, censored for those with epilepsy, and stratified by ASD diagnostic outcome.

Statistical significance was set at an alpha level = 0.05 and p-values were reported without adjustment for multiple comparisons. All statistical analyses were completed using SAS® statistical software version 9.4 (SAS Institute Inc., Cary, NC).

1.3 Results

1.3.1 Patient Characteristics

The number of participants evaluated at each timepoint is listed in Table 1. The largest number of participants was at the 12 month visit, which had 154 participants at the time of data analysis. The overall average age at time of enrollment was 5.6 ± 3.2 months. The majority of the patients were white, non-Hispanic (see Table 1 for complete distribution of race and ethnicity). Genetic testing results were available for 109 participants (TSC1= 15 (14%), TSC2= 82 (75%), No mutation identified= 12 (11%)). One-hundred seven out of 137 participants developed seizures by 36 months of age (78%), with an average age at seizure onset of 4.7 ± 3.3 months (range of zero to 22.5 months). Standard score means and standard deviations for the MSEL Early Learning Composite, PLS-5, and VABS-II Adaptive Behavior Composite are included in Table 1. Table 1 also lists frequency of seizure types. By 12 months and beyond, greater than 60% of the patients were prescribed vigabatrin. A total of 33 participants out 137 (24%) had a diagnosis of ASD at age 36 months.

1.3.2 Language predictors of ASP

Language and communication variables from the MSEL, VABS-II, and PLS-5 were used to determine which variables, if any, were associated with a diagnosis of ASD at 36 months (Figure 1). At 6 months, all language variables on the MSEL and PLS-5 were associated with an ASD diagnosis at 36 months. By 12 months, all language variables on the MSEL, PLS-5, and VABS-II were associated with an ASD diagnosis ($p \leq 0.01$).

The effect of language development on later ASD diagnosis was also looked at by dichotomizing DQ of each individual variable on the MSEL, VABS-II, and PLS-5 to determine how each individual score related to a later ASD diagnosis. Individuals with $DQ \geq 80$ were classified as normal whereas those with $DQ < 80$ were considered delayed (Figure 2). Interestingly, in the individuals with a $DQ < 80$, the number of children with and without an ASD diagnosis were approximately equal. As expected, in the individuals with a $DQ \leq 80$, a lower number of individuals had a diagnosis of ASD. We were also interested in determining if prediction of a diagnosis of ASD using individual language measures of the MSEL, VABS-II, and PLS-5 was independent of the child's overall global development. Therefore, we adjusted for overall development by using the Early Learning Composite standard score on the MSEL at each visit. Indicators of non-verbal learning on the MSEL, including visual reception and fine motor domains, are included in the MSEL. When accounting for overall level of development, several language variables at 18 and 24 months remained significant in predicting an ASD diagnosis (at 18 months VABS-II receptive language and expressive language, PLS-5 expressive communication and total language; at 24 months MSEL receptive language, VABS-II expressive language, all PLS-5 language variables). The visual reception domain on the MSEL was significant at 9 months, 18 months, and approached significance at 12 months for predicting a later ASD diagnosis.

1.3.3 Impact of Epilepsy as a Covariate on Language Development and ASD

Previous studies have shown that epilepsy impacts both language and development of ASD[4, 10, 12, 14, 15]; therefore, we sought to verify these relationships in our cohort and

further analyze the role that they play. Seizure frequency at 6 months of age was less helpful for predicting language and communication outcomes, whereas by 12 months and beyond higher seizure frequency negatively correlated with nearly every language and communication measure of the MSEL, VABS-II, and PLS-5 (Table 2). When viewing seizure onset as a continuous variable, age at seizure onset was associated with language scores in that later seizure onset was associated with higher scores in all communication variables on the MSEL, VABS-II, and PLS-5 (Table 3). Slopes (estimated increase for each one year increase in seizure onset) were all significantly greater than zero, ranging from 0.66 to 1.76 ($p < 0.05$). A Fisher's Exact analysis was performed to evaluate the relationship between seizure onset and a diagnosis of ASD at 36 months. The presence of seizures by 6 months of age was associated with an ASD diagnosis at 36 months ($p = 0.002$). A survival analysis using seizure onset as a continuous variable showed that individuals who were eventually diagnosed with ASD at 36 months exhibited earlier onset of seizures ($p < 0.0001$) (Figure 3). For those who did not have ASD, the median seizure onset was 6.5 months whereas seizure onset for the group with ASD was 4.3 months. An increase in seizure frequency was also associated with an ASD diagnosis at 36 months (OR 1.022, 95% CI 1.005-1.040, $p = 0.01$).

Among individuals with seizures, 30% (32/105) obtained an ASD diagnosis at 36 months versus 69% (73/105) who did not have ASD. In contrast only one patient (1/29; 3%) without epilepsy obtained an ASD diagnosis ($p = 0.002$).

Lastly, logistic regression analysis was performed to determine the relationship between language and ASD diagnosis when accounting for age at seizure onset. All MSEL, VABS, and PLS-5 language variables by 18 months of age appeared significantly related to a diagnosis of ASD at 36 months, even when accounting for epilepsy (Table 4). Prior to 18 months, language variables were not more significant than seizures. However, after 18 months, language variables became more of an indicator of who would go on to have diagnosis of ASD at 36 months compared to the presence of seizures.

1.4 Discussion

In this study, we sought to better understand language predictors of ASD in TSC, finding that direct observational assessment and parent reported measures of language during infancy and early childhood are both highly valuable in predicting a clinical diagnosis of ASD at 36 months in this high-risk population. Epilepsy severity (including seizure onset and frequency), which is highly prevalent in TSC at these same ages, was also confirmed to be associated with language delays and ASD. When accounting for age at seizure onset, by 12 months and beyond language was associated with an ASD diagnosis at 36 months.

Our findings are consistent with an earlier study by Jeste *et al.*, in which delays were found in all domains on the MSEL by 9 months of age in young children with TSC[7]. Additional studies have identified high prevalence of both cognitive deficits and ASD in older children and adults with TSC [13, 24, 25]. Our patients had a wide range of developmental scores with many in the average range, thus highlighting the variability in development in this young population. As expected, we found that individuals with worse language functioning

were more likely to be diagnosed with ASD. However, when controlling for overall development, we found that this relationship was less robust. However, at specific time points, particularly at 18 and 24 months, several language variables remained significant. It is also important to note that visual reception domain on the MSEL was a significant predictor of ASD at several time points, suggesting that this may be an area that needs to be monitored. Overall, results would indicate that language development could be a helpful adjunctive for overall development during infancy in TSC and that by measuring language we are able to adequately assess ASD risk without having to fully assess cognition, particularly early on. This is relevant for clinicians who are evaluating very young children with TSC in the clinic and may not have access to a full developmental battery. Studies focused on understanding the underlying pathophysiology of early language development, including social communication, in TSC and the mechanistic underpinnings tying language and epilepsy to ASD behaviors and traits would still require multimodal evaluation only provided by careful selection of complimentary assessment approaches and tools. However, early language screening could serve as a less costly and less time-intensive approach to identifying infants with TSC at risk for ASD, who then could be targeted for more definitive evaluation and/or therapeutic intervention. It should be noted, however, our findings do contradict an earlier study by Kenworthy *et al.*, who found that core language abilities had no impact on autism diagnosis but were rather representative of potential comorbid conditions that alter prognosis rather than diagnosis[26]. That study excluded patients with ASD with genetic or molecular etiologies, including TSC, so direct comparison of results is cautioned. For this analysis, we did not attempt to characterize ASD severity or probe specific subsets of ASD core behaviors.

Previous studies have shown that cognitive delay in children with TSC with epilepsy is evident by 12 months of age and that pediatric epilepsy is consistently associated with language delays[5]. However, studying these relationships in children this young is extremely difficult, likely because cognitive delays confound this relationship when assessed in a clinical setting. Within this study, we clarified the epilepsy-cognitive development relationship to include language development, in particular, as an aspect of development that consistently decreases with increased seizure burden defined by earlier age of seizure onset or increasing seizure frequency. We cannot conclude causality because we only track correlation, but the results indicate that both relate to worse language functioning.

Likewise, both earlier seizure onset and higher seizure frequency appear to be significantly related to a diagnosis of ASD. Using this same cohort, we previously reported that seizure onset prior to 12 months of age was significantly related to higher ADOS-2 scores[10], indicative of more severe autistic symptomatology. In the current analysis, earlier onset of seizures was significantly related to later ASD diagnosis. We also found that increased seizure frequency increased the likelihood of an ASD diagnosis at 36 months. It is important to note that both the direct measures of language (MSEL and PLS-5) and the parent report of language in everyday settings (VABS-II) were strongly related to seizure frequency. Therefore, these differences are not only something we are measuring in the more controlled environment of the clinic, but it is also impacting communication functioning in the real world.

In an attempt to understand the temporal relationship between language development, seizures, and development of ASD, we evaluated the ability of language scores to predict a diagnosis of ASD when accounting for the presence of epilepsy at each visit. Prior to 12 months, language does not provide any additional information over having epilepsy when determining a later diagnosis of ASD. However, by 18 months and beyond, language exerts an effect above the presence of epilepsy in individuals who will later get diagnosed with ASD at 36 months. This may be due, in part, because different domains of development are less differentiated during infancy, and assessment measures are likely less adept at differentiating language skills at such a young age. For the current analysis, we did not separate individuals based on seizure type or number of seizure types, nor did we take into account those who get better versus those who continue to have frequent seizures. By 12 months, we may have accounted for these differences, as in those who are having difficulty to control seizures by 12 months are likely to continue on this path. Plans for future analysis include analyzing these factors within the first 12 months and determining their impact.

Limitations to the present analysis include not accounting for natural and treatment-related variation in seizure frequency between visits and contribution of different seizure types to overall seizure burden, which could have additional impact on language and ASD outcomes. This is the focus of future analyses. In addition, only one individual with ASD did not have a history of seizures, which limits the ability to detect if language is an independent contributor to a diagnosis of ASD. However, due to the high percentage of seizures in TSC, this was expected. Our study was able to show, however, that a history of seizures alone does not predict risk for later development of ASD and that a history of epilepsy plus poor language may help improve our ability to predict at risk individuals and intervene sooner. It is also worth noting that our results for the frequency of ASD diagnosis were much lower than reported by others[5–8]. In our study, each participant underwent a rigorous assessment for ASD, which included administration of the ADOS-2 and ADI-R at both 24 and 36 months, along with longitudinal developmental assessments at multiple time points. Therefore, lower numbers may be reflective of a more stringent and thorough evaluation. In addition, we found that a higher proportion of individuals met ADOS-2 cut-off scores for ASD (40%) at both 24 and 36 months, but this did not reflect in the clinical diagnosis of ASD (24%). Further analysis is planned to examine the reasons for these differences.

1.5 Conclusion

Both epilepsy and language development are predictors of later diagnosis of ASD. Before 12 months, epilepsy status (onset and frequency), appears more effective for risk stratification. After 12-18 months, assessment of language development independently provides additional precision for predicting the likelihood of a diagnosis of ASD.

Acknowledgements:

We would like to acknowledge the TACERN Consortium and all of the individuals at each site that have been an integral part in performing assessments and clinical visits, as well as the research coordinators at each site.

Funding:

This research was supported by the National Institute of Neurological Disorders and Stroke (NINDS) of the NIH (U01-NS082320, P20-NS080199), the Tuberous Sclerosis Alliance, the Developmental Synaptopathies Consortium (U54NS092090), which is a part of the NCATS Rare Diseases Clinical Research Network (RDCRN). RDCRN is an initiative of the Office of Rare Diseases Research (ORDR), National Center for Advancing Translational Sciences (NCATS), funded through collaboration between NCATS, National Institute of Mental Health, NINDS and National Institute of Child Health and Human Development (NICHD). The study utilized clinical research facilities and resources supported by the NCATS of the National Institutes of Health Grant (UL1-TR000077 and UL1-TR000124).

Declaration of Interest:

JKC has received consulting fees and travel expenses from Roche. MS reports grant support from Novartis, Roche, Pfizer, Ipsen, LAM Therapeutics and Quadrant Biosciences unrelated to this project. He has served on Scientific Advisory Boards for Sage, Roche, Celgene and Takeda. DAK has received consulting and speaking fees and travel expenses from Novartis and additional research support from the National Institute of Neurological Disorders and Stroke of the NIH (U01-NS082320, U54-NS092090, P20-NS080199), the Tuberous Sclerosis Alliance, the Van Andel Research Institute, Novartis, and Upsher-Smith Pharmaceuticals. In addition he serves on the professional advisory board and international relations committee for the Tuberous Sclerosis Alliance and the editorial board of Pediatric Neurology. DAP has received research support from NIH (U01-NS082320; U54-NS092090; U01-NS092595); research support, consulting fees, and travel reimbursement from Curemark, LLC; and research support from Biomarin and Novartis. Joyce Wu receives grant support and serves on the Scientific Advisory Boards/Speakers' Bureaus for Novartis and Greenwich Biosciences/GW Pharmaceutical unrelated to this project. The remaining authors have no conflicts of interest.

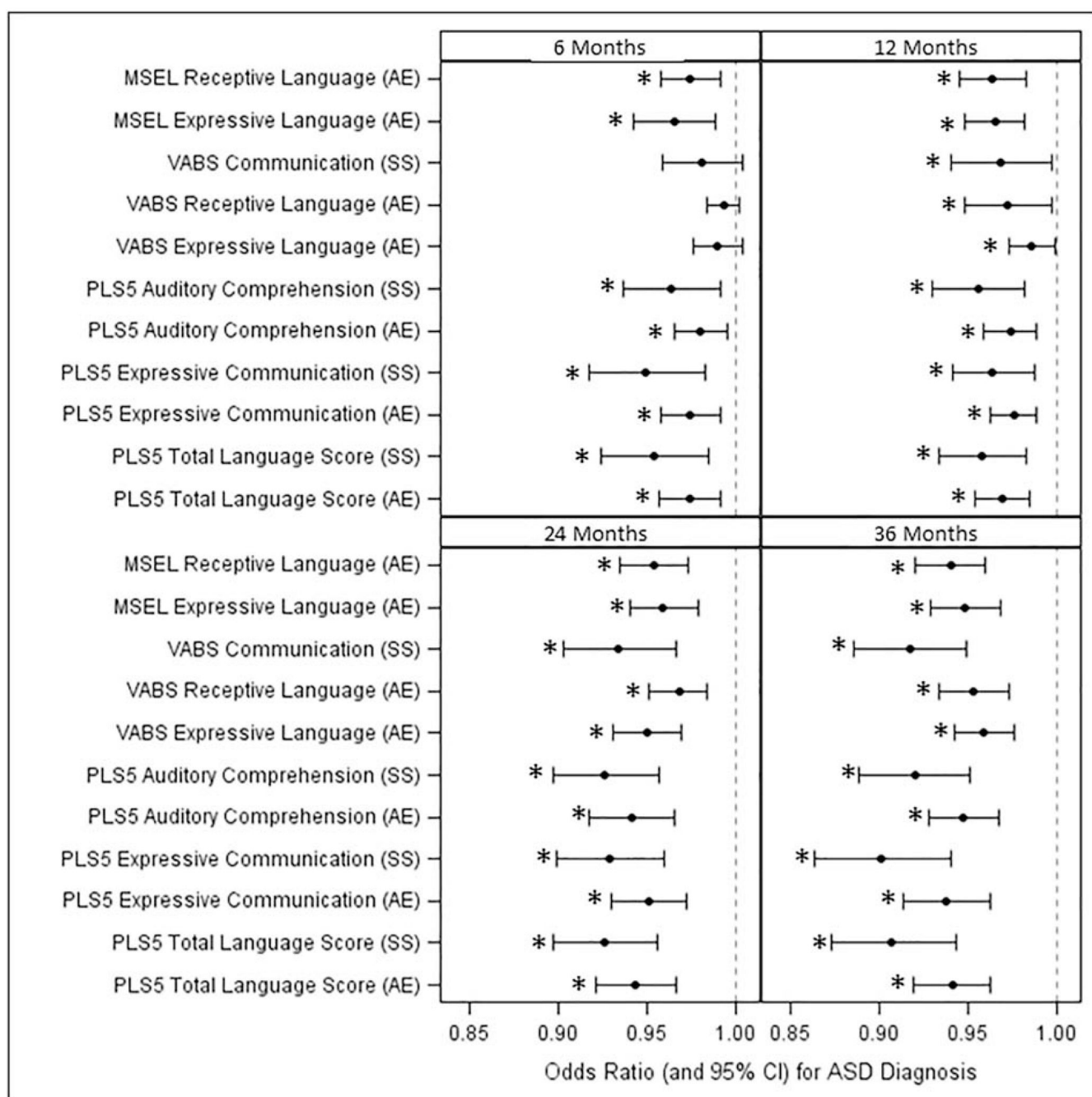
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HIGHLIGHTS:

- Both epilepsy and language development are predictors of later diagnosis of ASD
- Epilepsy is highly predictive of both language development and a diagnosis of ASD in young children with TSC
- Direct observational assessment and parent reported measures of language during infancy and early childhood are both highly valuable in predicting a clinical diagnosis of ASD at 36 months
- By 18 months and beyond, language exerts an effect above the presence of epilepsy in individuals who will later get diagnosed with ASD at 36 months

**Figure 1:**

Association between Language Variables and an ASD Diagnosis at 36 Months Legend-

Abbreviations: DQ= Developmental Quotient , SS= Standard Score , * = p<0.05



Figure 2:
Influence of Individual Language Scores on ASD Diagnosis at 36 Months Legend- All analyses had a p value of < 0.001

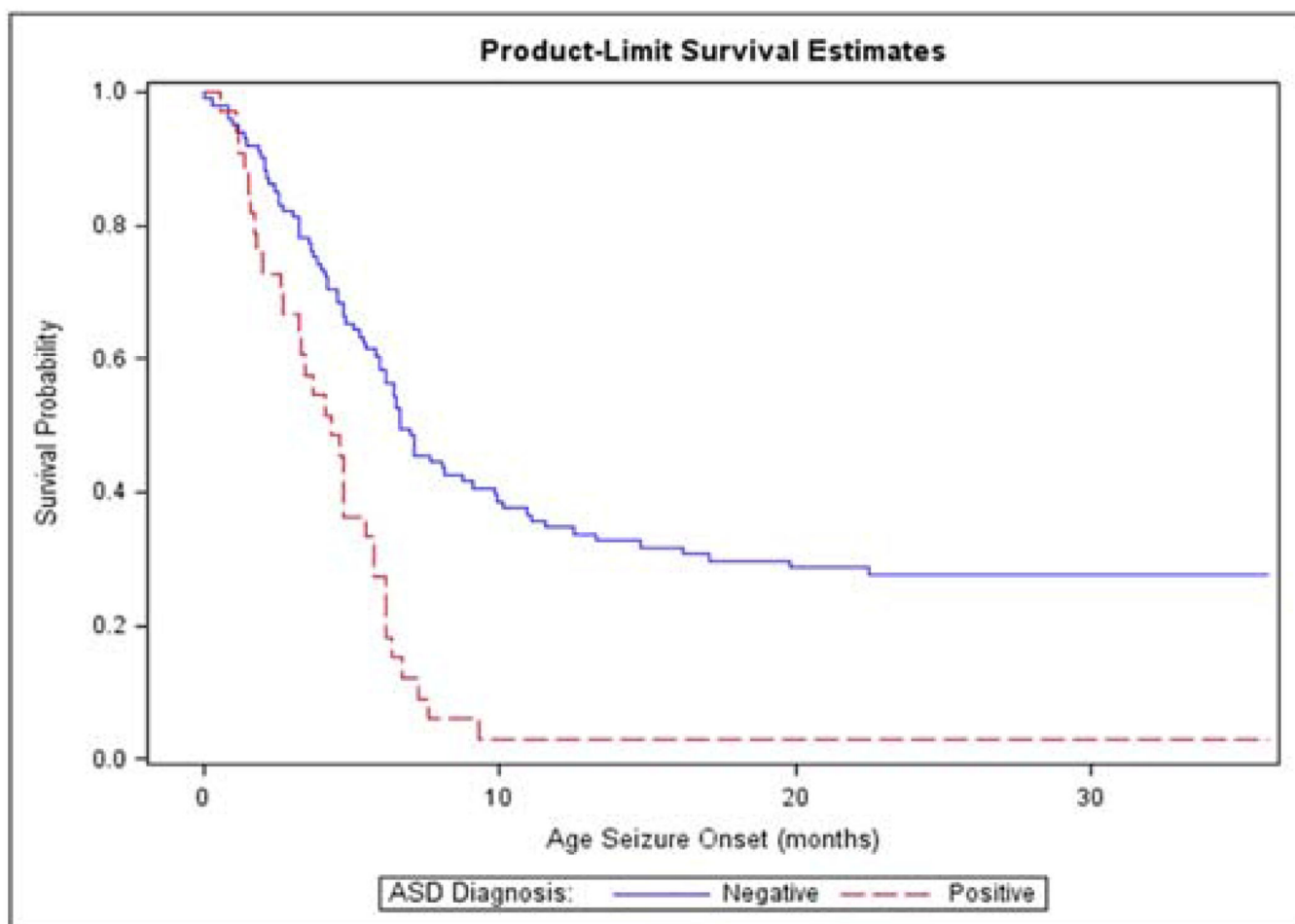


Figure 3.
Survival Analysis of Relationship between Seizure Onset and ASD Diagnosis

Table 1:**Patient Characteristics**

	6 months	9 months	12 months	18 months	24 months	36 months
Number of participants	111	143	154	144	139	137
Male;Female	48;62	70;73	76;75	73;71	70; 69	67; 70
Ethnicity						
Hispanic/Latino	24(22%)	29(20%)	30(20%)	30(21%)	27(19%)	26(19%)
Non-Hispanic/Latino	86(78%)	114(80%)	121(80%)	114(79%)	112(81%)	111(81%)
Race						
White	93(85%)	126(88%)	131(87%)	124(86%)	120(86%)	119(87%)
Black or African American	2(1.8%)	2(1.4%)	5(3.3%)	5(3.5%)	5(3.6%)	5(3.6%)
American Indian/Alaska Native	1(0.9%)	1(0.7%)	1(0.7%)	1(0.7%)	1(0.7%)	1
Asian	3(2.7%)	4(2.8%)	4(2.7%)	4(2.8%)	4(2.8%)	4(2.9%)
Other	4(3.6%)	3(2.1%)	3(2%)	3(2%)	2(2%)	2(1.5%)
Not reported	7(6.4%)	7(4.9%)	7(4.6%)	7(4.9%)	7(5%)	7(5.1%)
MSEL Early Learning Composite (mean $\pm$ SD) *	92.3 $\pm$ 17.9	87.6 $\pm$ 19	84.9 $\pm$ 19.5	81.2 $\pm$ 22.3	81.1 $\pm$ 24.1	81.4 $\pm$ 23.5
VABS-II Adaptive Behavior Composite (mean $\pm$ SD)	90 $\pm$ 14		86 $\pm$ 16.1	87.9 $\pm$ 15	88.2 $\pm$ 14.9	81.5 $\pm$ 16.2
PLS-5 Total Language Score (mean $\pm$ SD)	96.2 $\pm$ 16.8	88.5 $\pm$ 18.6	84.3 $\pm$ 18	87 $\pm$ 19.4	84.7 $\pm$ 19.7	79.6 $\pm$ 20.3
Medications at each visit (N)						
more than 1 AED	16	38	61	72	75	77
more than 2 AEDs	7	16	33	43	32	41
Seizure history						
Infantile Spasms	59	81	88	85	78	79
Focal Seizures	68	89	96	90	87	88
Generalized Seizures	16	20	22	19	18	22
Unclassified	8	12	13	11	11	10
> 1 Seizure Type	16	36	50	62	68	77
Non-pharmacological Therapies						
Physical	16	25	36	55	34	23
Occupational	7	23	34	60	33	35
Speech-language	1	6	16	44	48	53
Early Intervention	7	31	37	52	26	12
Applied Behavioral Analysis	0	0	2	2	5	10

Abbreviations: AED= anti-epileptic drug, SD= standard deviation

* The MSEL Early Learning Composite Standard Score was not attainable for all participants due to low developmental functioning. At 6 months= 92 participants; 9 months= 118 participants; 12 months= 122 participants; 18 months= 123 participants; 24 months= 113 participants; and 36 months= 95 participants had a valid standard score.

Table 2

Spearman Correlation Between Seizure Frequency and Communication variables

	6 months		12 months		18 months		24 months		36 months	
	r	p	r	p	r	p	r	p	r	p
Mullen Scales of Early Learning										
Expressive Language (DQ)	-0.28	0.02 *	-0.38	<0.0001 *	-0.4	<0.0001 *	-0.49	<0.0001 *	-0.44	<0.0001 *
Receptive Language (DQ)	-0.28	0.018 *	-0.41	<0.0001 *	-0.46	<0.0001 *	-0.59	<0.0001 *	-0.43	<0.0001 *
Vineland Adaptive Behavior Scales										
Communication Domain (SS)	-0.1	0.4	-0.44	<0.0001 *	-0.4	<0.0001 *	-0.52	<0.0001 *	-0.45	<0.0001 *
Expressive Language (DQ)	-0.05	0.7	-0.44	<0.0001 *	-0.39	<0.0001 *	-0.5	<0.0001 *	-0.49	<0.0001 *
Receptive Language (DQ)	-0.11	0.4	-0.35	<0.0001 *	-0.4	<0.0001 *	-0.52	<0.0001 *	-0.41	<0.0001 *
Preschool Language Scale-5										
Auditory Comprehension (DQ)	-0.16	0.2	-0.43	<0.0001 *	-0.45	<0.0001 *	-0.55	<0.0001 *	-0.44	<0.0001 *
Auditory Comprehension (SS)	-0.22	0.07	-0.44	<0.0001 *	-0.4	<0.0001 *	-0.53	<0.0001 *	-0.47	<0.0001 *
Expressive Communication (DQ)	-0.16	0.2	-0.45	<0.0001 *	-0.43	<0.0001 *	-0.53	<0.0001 *	-0.47	<0.0001 *
Expressive Communication (SS)	-0.23	0.06	-0.43	<0.0001 *	-0.41	<0.0001 *	-0.49	<0.0001 *	-0.47	<0.0001 *
Total Language (DQ)	-0.18	0.14	-0.47	<0.0001 *	-0.46	<0.0001 *	-0.56	<0.0001 *	-0.46	<0.0001 *
Total Language (SS)	-0.23	0.057	-0.48	<0.0001 *	-0.39	<0.0001 *	-0.54	<0.0001 *	-0.48	<0.0001 *

Abbreviations: SS= Standard Score, DQ= Developmental Quotient, r= Correlation Coefficient, p= p-value

*
=p<0.05

Table 3.

Relationship Between Seizure Onset and Language Outcomes

	Slope	Standard Error	P value
Mullen Scales of Early Learning			
Expressive Language (DQ)	1.32	0.37	0.0004 *
Receptive Language (DQ)	1.54	0.44	0.0006 *
Vineland Adaptive Behavior Scales			
Communication (SS)	0.86	0.28	0.002 *
Expressive Language (DQ)	1.63	0.48	0.001 *
Receptive Language (DQ)	1.43	0.64	0.03 *
Preschool Language Scale-5			
Auditory Comprehension (DQ)	1.76	0.48	0.0004 *
Auditory Comprehension (SS)	1.05	0.28	0.0002 *
Expressive Communication (DQ)	1.54	0.47	0.001 *
Expressive Communication (SS)	0.81	0.25	0.001 *
Total Language (DQ)	1.72	0.45	0.0002 *
Total Language (SS)	0.96	0.27	0.0004 *

Abbreviations: DQ= Developmental Quotient, SS=Standard Score

*
=p<0.05

Table 4:

Relationship between Language, Epilepsy, and ASD Diagnosis

Variables	6 Months		9 Months		12 Months		18 Months		24 Months		36 Months	
	OR (Lower CI-Upper CI)	p-value	OR (Lower CI-Upper CI)	p-value	OR (Lower CI-Upper CI)	p-value	OR (Lower CI-Upper CI)	p-value	OR (Lower CI-Upper CI)	p-value	OR (Lower CI-Upper CI)	p-value
Epilepsy (Yes vs No)	3.84 (1.11-13.27)	0.034 *	7.65 (1.68-34.88)	0.009 *	10.33 (1.31-81.38)	0.03 *	5.48 (0.67-45.23)	0.11	3.70 (0.74-18.51)	0.11	4.57 (0.50-42.20)	0.18
MSEL Receptive Language (DQ)	0.98 (0.96-1.00)	0.036 *	0.98 (0.96-1.00)	0.04 *	0.97 (0.95-0.99)	0.004 *	0.97 (0.95-0.99)	0.001 *	0.96 (0.94-0.98)	<.0001 *	0.94 (0.92-0.97)	<.0001 *
Epilepsy (Yes vs No)	4.55 (1.36-15.24)	0.014 *	8.71 (1.88-40.28)	0.006 *	9.13 (1.15-72.89)	0.037 *	6.24 (0.77-50.75)	0.09	5.10 (1.08-24.16)	0.04 *	6.48 (0.72-58.57)	0.10
MSEL Expressive Language (DQ)	0.97 (0.95-1.00)	0.018 *	0.99 (0.97-1.01)	0.43	0.97 (0.96-0.99)	0.002 *	0.96 (0.94-0.98)	0.0004 *	0.97 (0.95-0.99)	0.002 *	0.95 (0.93-0.97)	<.0001 *
Epilepsy (Yes vs No)	5.17 (1.57-17.06)	0.007 *			14.14 (1.79-111.55)	0.012 *	4.33 (0.51-36.77)	0.18	6.10 (1.28-29.19)	0.02 *	4.98 (0.58-42.58)	0.14
VABS Communication (SS)	0.99 (0.97-1.01)	0.37			0.99 (0.96-1.01)	0.32	0.92 (0.88-0.96)	0.0001 *	0.95 (0.92-0.98)	0.002 *	0.93 (0.90-0.96)	<.0001 *
Epilepsy (Yes vs No)	5.63 (1.71-18.48)	0.004 *			14.43 (1.85-112.31)	0.01 *	4.75 (0.57-39.58)	0.15	6.14 (1.30-29.04)	0.02 *	5.02 (0.58-43.45)	0.14
VABS Receptive Language (DQ)	0.1 (0.99-1.01)	0.39			0.99 (0.98-1.01)	0.24	0.96 (0.94-0.98)	0.0003 *	0.97 (0.96-0.99)	0.002 *	0.96 (0.94-0.98)	0.0002 *
Epilepsy (Yes vs No)	5.31 (1.62-17.33)	0.006 *			10.53 (1.32-83.81)	0.03 *	4.23 (0.49-36.70)	0.19	3.30 (0.65-16.84)	0.15	5.41 (0.64-46.03)	0.12
VABS Expressive Language (DQ)	0.99 (0.98-1.01)	0.4			0.98 (0.96-1.00)	0.03 *	0.95 (0.92-0.97)	<.0001 *	0.96 (0.94-0.98)	<.0001 *	0.97 (0.95-0.98)	0.0002 *
Epilepsy (Yes vs No)	4.15 (1.20-14.35)	0.025 *	7.65 (1.66-35.29)	0.009 *	10.36 (1.31-82.16)	0.03 *	6.67 (0.82-54.19)	0.08	0.93 (0.90-0.97)	<.0001 *	5.00 (0.56-44.44)	0.15
PLS5 Auditory Comprehension (SS)	0.98 (0.95-1.01)	0.13	0.98 (0.96-1.01)	0.20	0.97 (0.94-1.00)	0.03 *	0.96 (0.94-0.99)	0.005 *	3.68 (0.74-18.37)	0.11	0.93 (0.89-0.96)	<.0001 *
Epilepsy (Yes vs No)	3.90 (1.12-13.60)	0.033 *	6.91 (1.49-32.15)	0.01 *	10.23 (1.29-81.17)	0.03 *	5.35 (0.65-44.09)	0.12	0.95 (0.92-0.97)	<.0001 *	5.17 (0.60-44.44)	0.13
PLS5 Auditory Comprehension (DQ)	0.99 (0.97-1.00)	0.11	0.99 (0.97-1.00)	0.08 *	0.98 (0.97-1.00)	0.02 *	0.96 (0.94-0.98)	0.0004 *	4.92 (1.03-23.53)	0.046 *	0.95 (0.93-0.97)	<.0001 *
Epilepsy (Yes vs No)	4.49 (1.34-15.04)	0.015 *	6.89 (1.49-31.90)	0.01 *	11.05 (1.40-87.14)	0.02 *	5.87 (0.72-48.02)	0.10	0.94 (0.91-0.97)	0.0006 *	4.35 (0.51-37.30)	0.18

Variables	6 Months		9 Months		12 Months		18 Months		24 Months		36 Months	
	OR (Lower CI-Upper CI)	p-value	OR (Lower CI-Upper CI)	p-value	OR (Lower CI-Upper CI)	p-value	OR (Lower CI-Upper CI)	p-value	OR (Lower CI-Upper CI)	p-value	OR (Lower CI-Upper CI)	p-value
PLS5 Expressive Communication (SS)	0.96 (0.92-0.99)	0.015 *	0.97 (0.95-1.00)	0.08	0.98 (0.95-1.00)	0.05 *	0.96 (0.93-0.98)	0.0009 *	4.76 (1.00-22.79)	0.05 *	0.91 (0.87-0.95)	<.0001 *
Epilepsy (Yes vs No)	4.36 (1.29-14.68)	0.018 *	6.27 (1.35-29.24)	0.02 *	9.69 (1.22-76.80)	0.03 *	5.02 (0.61-41.44)	0.13	0.96 (0.94-0.98)	0.0003 *	4.54 (0.53-38.87)	0.17
PLS5 Expressive Communication (DQ)	0.98 (0.96-0.99)	0.009 *	0.98 (0.97-1.00)	0.03 *	0.98 (0.97-1.00)	0.01 *	0.96 (0.95-0.98)	<.0001 *	4.23 (0.86-20.80)	0.08	0.95 (0.92-0.97)	<.0001 *
Epilepsy (Yes vs No)	3.95 (1.16-13.47)	0.028 *	6.78 (1.46-31.45)	0.01 *	10.24 (1.29-81.03)	0.03 *	6.97 (0.86-56.47)	0.07	0.93 (0.90-0.97)	<.0001 *	4.13 (0.46-37.13)	0.21
PLS5 Total Language (SS)	0.97 (0.93-1.00)	0.037 *	0.98 (0.95-1.00)	0.07	0.97 (0.94-1.00)	0.02 *	0.97 (0.94-0.99)	0.008 *	4.08 (0.83-20.10)	0.08	0.91 (0.88-0.95)	<.0001 *
Epilepsy (Yes vs No)	3.70 (1.08-12.68)	0.038 *	5.89 (1.25-27.70)	0.02 *	8.41 (1.05-67.38)	0.04 *	4.65 (0.56-38.83)	0.16	0.95 (0.93-0.97)	<.0001 *	4.31 (0.50-37.39)	0.19
PLS5 Total Language (DQ)	0.98 (0.96-1.00)	0.026 *	0.98 (0.96-1.00)	0.02 *	0.98 (0.96-0.99)	0.003 *	0.96 (0.94-0.98)	<.0001 *	0.95 (0.92-0.97)	<.0001 *	0.95 (0.92-0.97)	<.0001 *

Abbreviations: DQ= Developmental Quotient, SS= Standard Score, OR= Odds Ratio, CI= Confidence Interval

* = p<0.05