Early Biomarkers of Autism Spectrum Disorder in Infants with Tuberous Sclerosis Complex

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Introduction: Tuberous Sclerosis Complex (TSC) is a rare, single-gene mutation, neurocutaneous disorder with high rates of comorbid autism spectrum disorder (ASD) and epilepsy. Epilepsy has previously been implicated in the development of TSC-associated ASD, but the role of language and the specific relationship between ASD, epilepsy, and language development in this population have not been determined.

Hypothesis: We predicted that physician and parent-reported measures of language at 6-9 months can significantly predict ADOS classification. Additionally, we hypothesized that seizure onset and frequency act as covariates in language development.

Methods: This study included 160 children aged 0-36 months enrolled in the TACERN (TSC and Autism Center of Excellence Research Network) database, a consortium of five hospital programs elucidating the TSC-ASD relationship. The Mullen Scales of Early Learning (MSEL), Vineland Adaptive Behavior Scales (VABS), and Preschool Language Scales, 5th Edition (PLS-5) assessed patients' language skills every 3-6 months from 6 months of age, and Autism Diagnostic Observation Scale (ADOS) classification at 24 and 36 months was our primary outcome.

Results: All but one of the MSEL variables exhibited significance in predicting ADOS classification at 6 months, a pattern only seen later with VABS and PLS-5. However, every language measure assessed was significantly negatively correlated with seizure frequency at as early as 18 months ($r=-0.37$ (± 0.09)). Delayed seizure onset was significantly positively correlated with language scores ($r=0.68$-1.95, $p<0.05$), and ADOS+ categorization at 36 months related to seizure onset before 9 and 12 months (OR=3.80; OR=5.13). Finally, ADOS+ classification significantly related to increased seizure frequency at 24 and 36 months (OR=1.13; OR=1.41).

Conclusions: The VABS and PLS-5 are largely insignificant and unnecessary for ASD risk stratification before 12-18 months. Additionally, seizure frequency, not just seizure onset, relates to ADOS scores and language development; therefore, treatment may help to mitigate the detrimental effects of epilepsy. While the specific nature of the relationships needs further research, epilepsy, language, and development of features of ASD appear integrally related in the TSC population.

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