Pediatric Neurology 75 (2017) 80–86

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Original Article

Utility of the Autism Observation Scale for Infants in Early Identification of Autism in Tuberous Sclerosis Complex

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ABSTRACT

BACKGROUND: Tuberous sclerosis complex (TSC) is a genetic disorder with high prevalence of associated autism spectrum disorder (ASD). Our primary objectives were to determine early predictors of autism risk to identify children with TSC in most need of early interventions. The Autism Observation Scale for Infants (AOSI) was evaluated as a measure of ASD-associated behaviors in infants with TSC at age 12 months and its ability to predict ASD at 24 months. **METHODS:** Children ages 0 to 36 months with TSC were enrolled in the TSC Autism Center of Excellence Research Network (TACERN), a multicenter, prospective observational study to identify biomarkers of ASD. The AOSI was administered at age 12 months and the Autism Diagnostic Observation Schedule-2 (ADOS-2) and Autism Diagnostic Interview-Revised (ADI-R) at 24 months. Developmental functioning was assessed using the Mullen Scales of Early Learning. Children were classified as ASD or non-ASD according to the ADOS-2. **RESULTS:** Analysis included 79 children who had been administered the AOSI at 12 months and ADOS-2 and ADI-R at 24 months. The ASD group had a mean AOSI total score at 12 months significantly higher than the non-ASD group (11.8 ± 7.4 vs 6.3 ± 4.7; $P < 0.001$). An AOSI total score cutoff of 13 provided a specificity of 0.89 to detect ASD with the ADOS-2. AOSI total score at 12 months was similarly associated with exceeding cutoff scores on the ADI-R. **CONCLUSIONS:** The AOSI is a useful clinical tool in determining which infants with TSC are at increased risk for developing ASD.

Conflicts of interest: JYW serves on the professional advisory board for the Tuberous Sclerosis Alliance; has received honoraria from and serves on the scientific advisory board and the speakers' bureau for Novartis Pharmaceuticals Inc and Lundbeck; and has received research support from the Tuberous Sclerosis Alliance, Novartis Pharmaceuticals Inc, Today's and Tomorrow's Children Fund, Department of Defense/Congressionally Directed Medical Research Program, and the NIH (U01NS082320, P20NS080199, R01NS082649, U54NS092090, and U01NS092595). MS is supported by Developmental Synaptopathies Consortium (U54 NS092090), which is part of the National Center for Advancing Translational Sciences (NCATS) Rare Diseases Clinical Research Network (RDCRN). His laboratory receives research funding from Roche, Novartis, and Pfizer, and he has served on the Scientific Advisory Board of Sage Therapeutics. In addition, he serves on the Professional Advisory Board of the Tuberous Sclerosis Alliance and is an Associate Editor of Pediatric Neurology. 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. HN currently has a project funded by BioMarin testing efficacy of an enzyme substitution drug for phenylketonuria (PKU). The remaining authors have no conflicts of interest.

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Article History:
Received May 8, 2017; Accepted in final from June 21, 2017

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0887-8994/$ — see front matter
http://dx.doi.org/10.1016/j.pediatrneurol.2017.06.010

Keywords: tuberous sclerosis complex, autism spectrum disorder, autism observational scale for infants, Autism Diagnostic Observation Schedule, infants, toddlers

Pediatr Neurol 2017;75:80–86

Introduction

Idiopathic autism spectrum disorder (ASD) affects 1% to 2% of the general population without a clear understanding of the underlying causes, which presents a major barrier to identifying at-risk infants and developing effective treatments to prevent or alter progression. ASD is typically diagnosed at an average age of four years.[1] However, parental concern has been shown to emerge during the child's first two years of life with language and communication problems most commonly reported.[2,3] In children who screened positive on the Modified Checklist for Autism in Toddlers (M-CHAT, M-CHAT-R) between 18 and 24 months, 93.4% of parents first reported developmental concerns at a mean age of 13.77 months.[4] These same children were subsequently diagnosed by clinical assessment with ASD or developmental delay 94.4% of the time. Additional studies have demonstrated a high correlation between parental concern and clinical assessments.[5,6] Despite recognizing concerns regarding ASD-specific behaviors, parents and clinicians often fail to recognize ASD as the diagnosis. This failure highlights the importance of the clinician's responsibility to validate parental concerns and perform timely objective assessments to make an appropriate diagnosis of ASD. The earlier this can be accomplished enables appropriate interventions and treatment strategies to be initiated when they offer the greatest potential for change.

Validated, formal assessment tools to identify ASD risk in infants are limited. The Autism Observation Scale for Infants (AOSI) was originally designed as a research tool to evaluate autism-specific behaviors in infants at elevated risk for developing ASD. The AOSI is a semi-structured assessment designed for infants ages six to 18 months, with 18 individual items meant to evaluate different areas of concern seen in children with ASD, including sensory and motor behaviors, attention, visual tracking, and social emotional behaviors.[7] Scores for each item are evaluator-judged and range from 0 to 3, with higher numbers indicating elevated ASD risk behaviors. Reliability of the AOSI was tested in high-risk infant siblings (had older siblings with ASD) at ages six, 12, and 18 months. Inter-rater reliability for individual items and total score were good to excellent, particularly at 12 months and beyond, and test-retest reliability at 12 months was acceptable.[7] Another study of infant siblings found that using both the AOSI at 18 months and Autism Diagnostic Observation Schedule (ADOS) at 36 months provided complementary information when making the diagnosis of ASD at age three years.[8] More recently, the AOSI was used clinically to evaluate early symptoms of ASD in high-risk infant siblings to determine the predictive ability of the AOSI to differentiate between high- and low-risk populations, as well as between those high-risk individuals who would eventually be diagnosed with ASD.[9] Comparing the AOSI at seven and 14 months and ADOS at 24 and 36 months, Gammer et al. found that children who were diagnosed with ASD scored significantly higher on the AOSI at 14 months than those who were not diagnosed with ASD even when accounting for developmental level.[9] Collectively, these results indicate that the AOSI may be useful to differentiate concerning features for ASD in high-risk infants, but understanding how coexistent developmental delays impact AOSI scoring for ASD-risk behaviors at younger ages and how those scores may be predictive of later diagnosis of ASD requires additional investigation.

Currently, no single factor has been identified as a consistent predictor of ASD; but single-gene disorders with a high prevalence of ASD, such as tuberous sclerosis complex (TSC), provide us with opportunities to investigate the underlying biology and identify potential treatments. TSC is a genetic disorder that affects multiple organ systems and is present in approximately 1 in 6000 individuals.[10] Retrospective and small pilot prospective studies have identified specific areas of cognitive impairment and autism spectrum behaviors in up to 50% of individuals with TSC.[11-14] A longitudinal cohort study compared differences between children with ASD with TSC to children with idiopathic ASD and found that syndromic ASD was similar to non-syndromic ASD in terms of their cognitive, behavioral, and social profiles.[15] Evaluation of the AOSI as an objective assessment tool to identify early ASD-associated behaviors in infants with TSC has been shown in a small prospective longitudinal cohort of infants,[13] but using the AOSI to predict later ASD risk in this population has not been previously reported. In 2012, we established the *TSC Autism Center of Excellence Research Network (TACERN)*, a large multicenter, prospective observational study to identify clinical, structural, and electrophysiological biomarkers predictive of ASD with the overall goal to establish an infrastructure for early detection of ASD and set the stage for future drug trials in patients with TSC who are at high risk for ASD. Our primary objectives are to determine the earliest age at which autism risk behaviors can be detected in order to identify those children in most need of accessing autism-specific interventions. Here we analyze the suitability of using the AOSI as an objective measure of ASD-associated behaviors in infants with TSC at 12 months of age and the ability of the AOSI to predict meeting ASD criteria on the ADOS-2 at 24 months of age.

Materials and Methods

Subject recruitment

Children ages 0 to 36 months with TSC were enrolled into TACERN (*clinical* trials.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). Institutional Review Board approval was obtained at each of the five sites, and informed consent was acquired from all participating families before enrollment.